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GEOGRAPHICAL VARIATION IN LEUKAEMIA MORTALITY IN RELATION TO BACKGROUND RADIATION AND OTHER FACTORS

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There is no doubt that the risk of developing leukaemia can be increased by exposure to ionizing radiations, but it is not clear whether this effect is produced by all types of exposure or whether it is limited to certain levels of dose and of dose-rate. Cases have been produced by exposure of the whole body to doses of γ rays of the order of 100 to 500 rads given within a few seconds as a result of the explosion of atomic bombs (Folley, Borges, and Yamawaki, 1952; Lange, Maloney, and Yamawaki, 1954; Medical Research Council, 1956; Wald, 1958) and by partial body-exposure to x rays given at rates of 10 to 50 rads per minute in the course of radiotherapy (Court Brown and Doll, 1957; Simpson and Hempelmann, 1957). In most of the latter cases substantial amounts of active marrow may be presumed to have received total doses of at least 100 rads. The evidence to implicate smaller doses, such as are used in diagnostic radiography, is less complete (March, 1950; Stewart, Webb, and Hewitt, 1958; Faber, 1958); but if these doses are leukaemogenic, it may be because the rates at which they are given are similar to those used in radiotherapy. It does not necessarily follow that a similar effect would be produced by ionizing radiations given at much lower rates. Even if a dose of 1 rad given in 1 second or 1 minute carries some leukaemogenic risk, there may not be any risk from exposure to the same dose spread over about 10 years—that is, given at the average dose-rate of natural background radiation.

Doses given at very low dose-rates may, however, be presumed to produce mutations in marrow cells comparable to the gene mutations in germ cells, and if such mutations are capable of playing any part in the development of cancer the possibility would have to be considered that the natural background radiation might also be responsible for some cases of leukaemia. Lewis (1957) has argued that the present evidence of the relationship between dose and incidence implies that background radiation may produce about 10 to 20% of the cases of leukaemia that occur in the U.S.A. Others (Brues, 1958; Lamerton, 1958; Mole, 1958) disagree, and some think that the evidence from animal experiments weighs heavily against the possibility that any cases could be produced by irradiation of such low intensity.

It is difficult to make direct observations of the effect of background radiation, because any effect is likely to be small in comparison with that due to other causes. Populations of the order of hundreds of thousands would have to be studied, and it is difficult to maintain the same standards of diagnosis throughout such large populations. The present study was therefore undertaken with some misgiving; but it was thought that an attempt to measure the effect should be made—if only to demonstrate its impracticability. Scotland seemed to be a favourable area to study because: (1) it contains two contrasting cities, each of approximately 180,000 inhabitants, with similar geographical situations and each containing a medical school, but built out of different material and likely to provide a substantial difference in background radiation; (2) the population is fairly stable and many people reside in the same town throughout their life; (3) the Registrar-General for Scotland had provided us with copies of all death entries relating to leukaemia for the years 1939–56, inclusive, in the course of another investigation.

Method

The country was divided into 10 areas: the two cities referred to previously (Aberdeen and Dundee) and the two surrounding rural areas (Aberdeenshire and Angus

and Kincardine); two other large cities (Edinburgh and Glasgow); three largely rural areas covering the remainder of the northern, western, and central regions; and one large area—the rest of Scotland—comprising the whole region south of Perthshire less Edinburgh and Glasgow. Accurate counts of the population by sex and age had been made for each of the 10 areas on two occasions during the period studied—in September, 1939, when the population was required to register for the purposes of identification, and at the 1951 census. Estimates of the populations in 10-year age-groups were obtained from the Registrar-General for 1956 and estimates for intervening years were made by simple arithmetical interpolation. In view of the distortion of the population by military service during the war, the estimates for this period are certainly inaccurate, and the results have therefore been analysed separately for 1939–46 and 1947–56. By 1947 the great majority of men in the armed Forces had been demobilized, and the population estimates for the second period are believed to be reasonably accurate. The inaccuracy in the earlier period is unlikely to be important as it must have affected all the 10 areas and is unlikely to have created a significant bias in favour of one.

The deaths were classified according to the area of usual residence; persons in the armed Forces or normally resident abroad were excluded. The causes of death were initially classified in nine groups—acute, chronic, and unspecified lymphatic leukaemia; acute, chronic, and unspecified myeloid leukaemia; other and unspecified acute leukaemia; chronic unspecified leukaemia; and leukaemia without other specification. Estimates of the total numbers of deaths likely to have been due to acute leukaemia, chronic myeloid leukaemia, and chronic lymphatic leukaemia were then obtained by allocating the unspecified cases to one or other of these three groups by assuming that for each sex and in each 10-year age-group the proportions of the various types were the same as those recorded when the types were specified. A detailed account of the method is given in a report on the changes in leukaemia mortality in England and Wales (Court Brown and Doll, 1959).

Sex and age-specific mortality rates for each of the three main types of leukaemia and for all leukaemia were calculated for all Scotland for the two periods 1939–46 and 1947–56. The expected numbers of deaths in each of the 10 areas from each type of leukaemia were then calculated by multiplying the observed rates for all Scotland by the estimated populations in each sex and 10-year group in each area. Finally, the observed deaths in each area were classified in the nine original diagnostic groups and the numbers attributed to acute leukaemia, chronic myeloid leukaemia, and chronic lymphatic leukaemia were estimated by assuming that the proportions of the various types among the unspecified cases were the same, in each age and sex group, as the proportions recorded in the same area when the types were specified.

Estimates of the expected numbers of deaths and of the observed numbers attributable to the three main types of leukaemia were confined to persons aged 15 years and over as it was thought that this age-group would be the most likely to show any effect due to background radiation. Adults would have had opportunity of accumulating a greater dose from background sources, and there are reasons for thinking that much childhood leukaemia, which has a peak mortality at age 3 years, is due to environmental factors that have become common only in the past 30 years.

Measurements of the natural background radiation were made in four areas. The surveys covered two predominantly granite districts—Aberdeen City and Aberdeen County—and two districts of sedimentary rocks—Edinburgh and Dundee. In all four areas most of the houses and buildings are made of local stone, so that a sufficient homogeneity exists to give significance to a mean population dose-rate.

Measurements of gamma-ray dose-rate were made out-of-doors and in houses. The houses, found by private inquiry, numbered 155 in Edinburgh, 103 in Aberdeen, and 71 in Dundee. They were distributed in reasonably representative patterns over the built-up areas of the cities and included the various types of building material in proportions closely following the statistics provided by the city surveyors. Approximately the same numbers of measurements were made on roads and pavements.

In Aberdeenshire the distribution of the 172 houses in which measurements were made had to be arranged to take into account the variations in population density and local geology. The survey included all the 10 parishes or boroughs with populations of 3,000 or more; 4 out of the 10 parishes with populations between 2,000 and 2,999; 5 out of the 23 parishes with populations between 1,000 and 1,999; and 8 out of 39 parishes having populations less than 1,000. A procedure of random selection, with some stratification as to region, was adopted for parishes of less than 3,000 population, and in all groups the numbers of houses selected lay between 10 and 14 per 1,000 inhabitants.

The measurements were made with a portable high-pressure ionization chamber, having the required sensitivity and long-term stability (Spiers, 1959); a single observation, with an ion-collection time of about three minutes, carried a standard error of $\pm 1.5\%$. At each out-of-door site two measurements were made, and in houses two measurements were made at each of three selected points—in the living-room, kitchen, and one upstairs bedroom. The mean of the six indoor measurements was taken as typical of the house dose-rate. In single-floor flats only two rooms were measured. The cosmic-ray response of the instrument, corrected to allow for overhead shielding, was subtracted from the reading at each site before applying an appropriate gamma-ray calibration factor to derive the local gamma-ray dose-rate.

Results

Leukaemia Mortality

The numbers of deaths attributed to leukaemia among adults in each of the 10 areas studied and the numbers expected on the basis of the leukaemia mortality for all Scotland are shown in Table I; they are shown separately for men and for women and for each of the periods 1939–46 and 1947–56. The differences between the numbers of deaths observed and expected in each area are statistically highly significant ($\chi^2=51.94$; $n=9$; $P<0.001$). In two of the areas—Aberdeen and Edinburgh—the differences are large and are likely to

TABLE I.—*Number of Deaths Attributed to Leukaemia in Various Parts of Scotland* (1939–56) *Compared with the Number Expected on the Basis of the Scottish National Mortality* (*Persons Aged* 15 *Years and Over*)

Area	No. of Deaths Among Men				No. of Deaths Among Women				Total No. of Deaths	
	1939–46		1947–56		1939–46		1947–56			
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
Aberdeen	18	16·0	45	31·2	22	15·3	49	29·5	134	92·0
Dundee	11	15·7	38	29·8	12	15·2	33	29·1	94	89·8
Edinburgh	59	43·6	100	83·9	61	40·5	85	78·2	305	246·3
Glasgow	85	103·9	162	187·3	74	81·9	142	156·6	463	529·7
Aberdeenshire	18	14·3	21	26·6	15	11·5	27	21·5	81	73·9
Angus and Kincardine	15	12·6	24	23·8	9	11·5	19	20·8	67	68·7
Banff, Inverness, Moray, and Nairn	11	19·2	50	35·9	14	16·0	34	28·9	109	100·0
North Scotland	14	15·6	27	27·7	12	13·3	19	22·2	72	78·8
Perthshire	16	13·0	26	24·9	14	12·1	34	21·8	90	71·8
Rest of Scotland	241	234·0	422	444·0	172	187·6	327	360·5	1,162	1,226·1
All Scotland	488	487·9	915	915·1	405	404·9	769	769·1	2,577	2,577·0

TABLE II.—*Standardized Mortality Ratios for Leukaemia in Various Parts of Scotland, for Men and for Women and for the Periods* 1939–46 *and* 1947–56 (*Persons Aged* 15 *Years and Over*)

Area	Standardized Mortality Ratio for:				
	Men	Women	1939–46	1947–56	All Persons 1939–56
Aberdeen	133	158	128	155	146
Dundee	108	102	74	121	105
Edinburgh	125	123	143	114	124
Glasgow	85	91	86	88	87
Aberdeenshire	95	127	128	100	110
Angus and Kincardine	107	87	100	96	98
Banff, Inverness, Moray, and Nairn	111	107	71	130	109
North Scotland	95	87	90	92	91
Perthshire	111	142	120	128	125
Rest of Scotland	98	91	97	93	95
All Scotland	100	100	100	100	100

be attributable to chance.* In Table II, standardized mortality ratios—that is, the observed numbers of deaths expressed as percentages of the numbers expected—are given for men and for women and for all persons for each period. The data show that in Aberdeen the ratio was the highest recorded both for men and for women, it was the highest recorded in the period 1947–56 and was the second highest (equal to that in Aberdeenshire) in the period 1939–46. In Edinburgh, the mortality ratio was the second highest recorded for men and the fourth highest for women; it was the highest recorded in the period 1939–46, but was only slightly above average in 1947–56.

*The contributions to χ^2 are respectively 19.17 and 14.06. In Perthshire the proportionate excess is slightly greater than in Edinburgh, but the expected number of deaths is much smaller and the difference may be regarded as a chance finding (contribution to χ^2, 4.64).

In Table III the results are shown separately for acute leukaemia, chronic myeloid leukaemia, and chronic lymphatic leukaemia; because of paucity of numbers in some of the groups the data are shown only for all persons and for the whole period 1939–57. Standardized mortality ratios are shown in Table IV. The data show that the excess mortality in Aberdeen has been principally due to an excess of acute leukaemia and of chronic myeloid leukaemia, while the excess mortality in Edinburgh has been due principally to an excess of chronic lymphatic leukaemia.

The total leukaemia mortality in Aberdeen and in Edinburgh is shown for three separate age-groups in Table V. The observed mortality is seen to have been greater than expected at all adult ages in Aberdeen, but in Edinburgh the excess is limited to ages 35 years and over.

TABLE IV.—*Standardized Mortality Ratios for Acute, Chronic Myeloid, and Chronic Lymphatic Leukaemia in Various Parts of Scotland,* 1939–56 (*Persons Aged* 15 *Years and Over*)

Area	Standardized Mortality Ratios for:			
	Acute Leukaemia	Chronic Myeloid Leukaemia	Chronic Lymphatic Leukaemia	All Leukaemia
Aberdeen	161	142	117	146
Dundee	95	103	125	105
Edinburgh	113	113	154	124
Glasgow	94	80	80	87
Aberdeenshire	121	94	100	110
Angus and Kincardine	89	84	124	98
Banff, Inverness, Moray, and Nairn	117	87	112	109
North Scotland	84	132	72	91
Perthshire	142	96	121	125
Rest of Scotland	92	103	92	95
All Scotland	100	100	100	100

TABLE III.—*Numbers of Deaths Attributable to Acute, Chronic Myeloid, and Chronic Lymphatic Leukaemia in Various Parts of Scotland* (1939–56) *Compared with the Numbers Expected* (*Persons Aged* 15 *Years and Over*)

Area	No. of Deaths from Acute Leukaemia		No. of Deaths from Chronic Myeloid Leukaemia		No. of Deaths from Chronic Lymphatic Leukaemia		Total No. of Deaths	
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
Aberdeen	77·5	48·0	29·2	20·6	27·3	23·3	134	92·0
Dundee	44·5	46·6	20·8	20·2	28·7	23·0	94	89·8
Edinburgh	143·5	126·6	62·7	55·5	98·8	64·1	305	246·2
Glasgow	264·8	281·9	93·0	116·7	105·3	131·0	463	529·7
Aberdeenshire	46·0	37·9	15·3	16·3	18·7	19·7	81	73·9
Angus and Kincardine	31·0	34·7	13·0	15·4	23·0	18·6	67	68·7
Banff, Inverness, Moray, and Nairn	60·1	51·2	19·2	22·1	29·8	26·7	109	100·0
North Scotland	32·8	38·9	23·2	17·6	16·1	22·3	72	78·8
Perthshire	51·1	36·1	15·4	16·1	23·5	19·5	90	71·8
Rest of Scotland	592·6	641·8	279·7	270·9	289·6	313·4	1,162	1,226·1
All Scotland	1,343·9	1,343·7	571·5	571·4	661·8	661·6	2,577	2,577·0

TABLE V.—*Comparison Between the Numbers of Deaths from Leukaemia Observed and Expected in Aberdeen and Edinburgh, by Age (Persons Aged 15 Years and Over)*

Age (Years)	Aberdeen			Edinburgh		
	No. of Deaths		Observed Deaths as % of Expected	No. of Deaths		Observed Deaths as % of Expected
	Observed	Expected		Observed	Expected	
15–34	23	16·6	139	36	40·7	88
35–54	38	27·0	141	92	70·6	130
55+	73	48·4	151	177	134·9	131
All ages	134	92·0	146	305	246·2	124

Background Radiation

The dose-rates out-of-doors in Edinburgh, Dundee, and Aberdeen are shown in Fig. 1. The mean dose-rate of 104 m.rad per year in Aberdeen is more than twice the mean of 48.5 m.rad per year in Edinburgh. Fig. 2 shows that the dose-rates in the stone houses in the three cities are also different, the mean dose-rate in the Aberdeen granite houses being 87 m.rad per year compared with 48.5 m.rad per year in sandstone houses in Edinburgh. Though no exact analysis has been made, the difference in dose-rate between the Dundee (Old Red) and the Edinburgh (Lower Carboniferous) sandstone houses is in keeping with the higher potash content of the Dundee stone (C. F. Davidson, 1959, personal communication).

The results of the out-door measurements in Aberdeen show the interesting feature that the mean dose-rates over half-mile annular zones increase steadily from 75 m.rad per year in the peripheral zone (2½ to 3 miles radius) to 115 m.rad per year in the central zone.

The dose-rates measured in the survey of the county of Aberdeen are shown in Figs. 3 and 4. Each histogram shows a greater spread of dose-rates than is seen in the results for the cities because much greater variation exists in surface geology and in the materials used for constructing roads and houses.

In each of the four areas the average dose-rate out-of-doors is taken as the mean of all the outdoor observations. In the three cities a mean indoor dose-rate is obtained by weighting, according to the proportions of houses of different types. In Aberdeen County mean dose-rates are derived for each population group surveyed, and a final average dose-rate for the whole population is obtained by weighting the mean dose-rate for each group by the proportion of the total population it represents.

The dose-rates in this report have so far related to measurements in air. In order to determine mean dose-rates to the bone-marrow, it is necessary to introduce (1) attenuation factors for overlying tissues, (2) a time factor to allow for the length of time exposed to indoor and outdoor radiation, and (3) the additional dose-rate from cosmic rays and internal sources.

The attenuation factor for bone-marrow has been derived from measurements in a water-filled model irradiated by a nearly omnidirectional array of radioactive sources. These measurements were made at several points on the surface and within the model, and covered a range of gamma-ray energies (Spiers and Overton, 1960). With the use of data on the distribution of red marrow in the body (R. E. Ellis, 1958, personal communication) a mean attenuation factor was derived at a gamma-ray energy approximating to that of background radiation. The value of 0.64 for this mean attenuation factor corresponds to a mean marrow depth of about 4 cm. from the body surface.

The time factor has been assumed to be 0.25 for outdoor radiation and 0.75 for indoor radiation—that is,

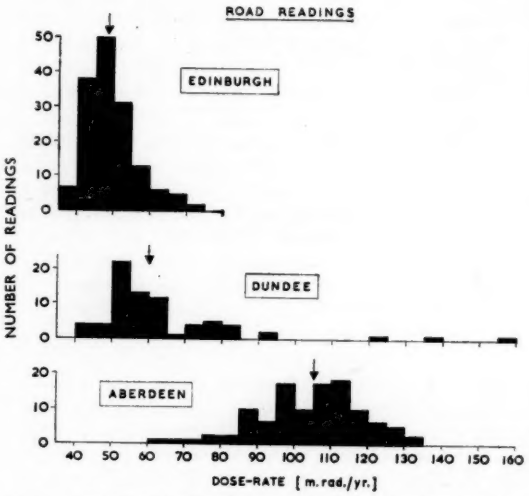

FIG. 1.—Background radiation out-of-doors in Aberdeen, Dundee, and Edinburgh.

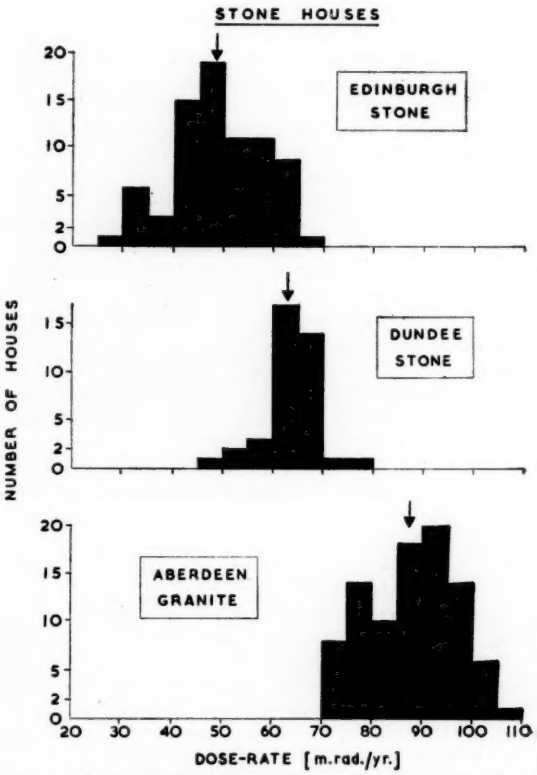

FIG. 2.—Background radiation inside stone houses in Aberdeen, Dundee, and Edinburgh.

it has been assumed that on average six hours a day are spent outdoors.

Cosmic rays and potassium-40 contribute most of the dose-rate from natural sources, additional to the local gamma radiation. The cosmic-ray dose-rate averaged for time spent indoors and out-of-doors amounts to approximately 24 m.rad per year to the bone-marrow. In trabecular bone the average potassium content may be expected to lie between 0.05% for mineral bone and a value near to 0.2% for the marrow; a mean dose-rate of 15 m.rad per year may be taken as sufficiently representative. Small additional dose-rates from carbon-14 and radon bring the total internal dose-rates to 43 m.rem per year.

The data in Table VI show the contributions made by these various factors and the total annual doses to the bone-marrow for populations in the four areas investigated. The mean dose-rates for the four areas have standard errors of approximately 1% and the difference in the mean bone-marrow dose-rates to the populations of Aberdeen and Edinburgh is 21 ± 0.6 m.rad per year. If a shorter period of three hours is assumed to be spent out-of-doors per day the difference in the population dose-rates in Aberdeen and Edinburgh is reduced to 18.5 m.rad per year. Certain systematic errors in instrument calibration, attenuation factor, allowance for cosmic rays, etc., are common to the measurements in all four areas: the values of the dose-rates in absolute units have a limiting error of about $\pm 3.5\%$.

TABLE VI.—*Mean Bone-marrow Dose-rates from Background and Internal Radiation in Four Parts of Scotland*

Type of Radiation	Mean Dose-rate in m.rad per Year in:			
	Edinburgh	Dundee	Aberdeen-shire	Aberdeen
Local gamma radiation, measured in air:				
Out-of-doors	48·5	63·0	69·5	104·0
In houses	60·0	67·2	81·5	85·3
24-hour average	57·1	66·2	78·5	90·0
Total radiation to bone-marrow:				
Local gamma radiation	37	43	50	58
Other background and internal sources	43	43	43	43
Total dose	80	86	93	101

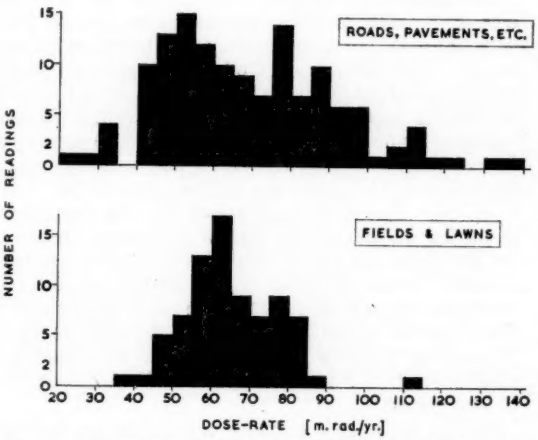

FIG. 3.—Background radiation out-of-doors in Aberdeenshire (excluding Aberdeen City).

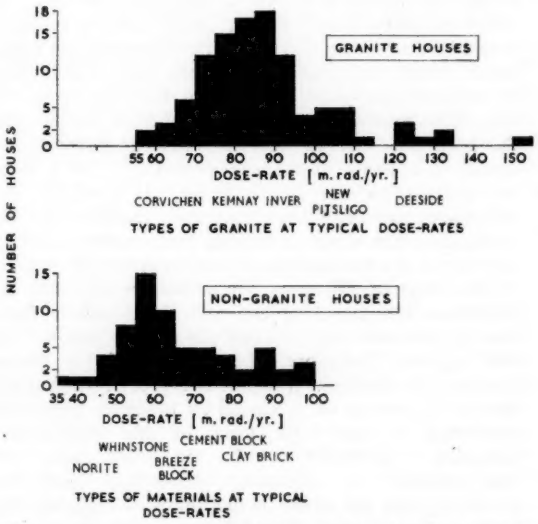

FIG. 4.—Background radiation indoors in Aberdeenshire (excluding Aberdeen City).

The differences will have been underestimated slightly as a result of the increase during the survey of local gamma radiation due to fall-out. The measurements were made in Aberdeen in August, 1958; in Dundee in October, 1958; in Edinburgh in February 1959; and in Aberdeenshire in August, 1959. Between the surveys in Aberdeen and Edinburgh the dose-rate over undisturbed grassland in Leeds rose by about 3 m.rad a year (Spiers, 1959). It is, however, improbable that the dose-rates over tilled land, hard surfaces of roads and pavements, and in houses have increased to the same extent. Measurements made at 12 road points in the 1958 road survey were repeated in 1959, and the difference between the mean dose-rate on the two occasions was less than its standard error, which—for this small number of measurements—was 2 m.rad per year.

A more detailed account of the results of the survey will be published elsewhere (Spiers and McHugh, 1960).

Comparison Between Mortality and Background Radiation

Estimates of the average marrow-dose received per annum from all natural sources are shown in Table VII in comparison with the standardized mortality ratios for acute leukaemia and chronic myeloid leukaemia combined—that is, for the two types of leukaemia that are known to be capable of being produced by ionizing radiations. The Table shows that the ranking order is the

TABLE VII.—*Comparison Between Average Radiation Dose to Bone-marrow and Mortality from Acute Leukaemia and Chronic Myeloid Leukaemia in Four Parts of Scotland (Persons Aged 15 Years and Over)*

Area	Average Dose to Bone-marrow (m.rad/Year)	Acute Leukaemia and Chronic Myeloid Leukaemia	
		Standardized Mortality Ratio	Standardized Death Rate per Million Persons per Year
Aberdeen	101	155	46
Aberdeenshire	94	113	33
Dundee	86	98	29
Edinburgh	80	113	33

same for both measurements in three of the four areas; but in one area the mortality ratio is the second highest, whereas the bone-marrow dose is the lowest. The Table shows also that the difference in mortality is substantially greater than the difference in the estimated marrow-dose. The best comparison is perhaps between Aberdeen and Dundee, since these towns are similar in many respects apart from the features associated with the level of background radiation. Comparison of the data for these towns shows that the recorded mortality is 50–60% higher in Aberdeen, whereas the marrow dose is only 17% higher.

Discussion

Examination of leukaemia mortality in Scotland shows that substantial differences are recorded in different areas. Some of these differences are presumably due to random fluctuation; but other factors are needed to account for the high mortality in Aberdeen and Edinburgh. Present knowledge suggests that these may include (1) the completeness of case-finding, (2) economic status, and (3) exposure to ionizing radiations.

The diagnosis of leukaemia is relatively sophisticated and many cases are likely to be missed unless pathological services are readily available. Much of the increase in leukaemia mortality in Britain over the past 30 years has been attributed to improved case-finding, and it has been suggested that this is particularly important as an explanation of the very great increase in the mortality from chronic lymphatic leukaemia that has occurred in the older age-groups (Court Brown and Doll, 1959). It may therefore be thought that the excess mortality in Edinburgh, which is mostly attributable to chronic lymphatic leukaemia and is limited to ages 35 years and over, is principally due to this factor. Since Edinburgh is a capital city with a high standard of living and a large and world-famous medical school this is not unreasonable. The same factor may also account to some extent for the excess mortality recorded in Aberdeen. The last two professors of medicine have had a special interest in haematology, and it is possible that their precept and example have resulted in a greater awareness of the possibility of the diagnosis. It should, however, be noted that the first of them subsequently became professor of medicine in Edinburgh in 1938 and that in 1947–8 the Aberdeen mortality was much higher that that recorded in Edinburgh. Moreover, in contrast to the experience in Edinburgh, the Aberdeen mortality was higher than expected at all adult ages, and the excess was primarily due to a high incidence of acute leukaemia and chronic myeloid leukaemia.

High economic status has been found to be associated with a high leukaemia mortality in several studies in Britain (Registrar-General of England and Wales, 1938, 1958) and in the U.S.A. (MacMahon, 1957). In the period 1930–2 the standardized mortality ratio for leukaemia (combined at that time with Hodgkin's disease) was 153 in social class I (business executives and higher professions) and 85 in social class V (unskilled labourers). In 1949–53 the ratios for leukaemia alone were respectively 123 and 89. The reason for the high mortality in the wealthier strata is unknown; it may be no more than a reflection of the effect of better case-finding and, perhaps, a greater exposure to ionizing radiations; but, whatever the explanation, the factors responsible for it may be presumed to have contributed to the excess in Edinburgh—a capital city with a high proportion of professional, administrative, and clerical workers—and to account for some of the deficiency in the crowded industrial city of Glasgow. There is, however, no reason to suppose that social class factors *per se* should have contributed to an abnormal incidence of leukaemia in Aberdeen.

The effect of differences in exposure to ionizing radiation is difficult to assess. Published estimates of the risk associated with low doses have been obtained by extrapolation from data for patients given radiotherapy for ankylosing spondylitis and for persons exposed to the atomic explosions in Hiroshima and Nagasaki. Whether it is justifiable to extrapolate over so large a range of total dose and of dose-rate is open to doubt, but there is no reason to suppose that the leukaemogenic effect of small doses on a normally susceptible population could be much more than proportional to the total dose, and the estimates may be used to provide an upper limit to the number of cases which are likely to be produced.

According to Lewis (1957) the risk per rad is likely to be of the order of 2 cases per million persons per year (with upper and lower limits of 0.7 and 6.0 cases per million per year.) Court Brown and Doll (1957) suggested that the risk per rad might lie within the range of 1.0 to 1.6 cases per million persons per year, and the United Nations Scientific Committee (United Nations, 1958) estimated the risk on the assumption that 1 rem would produce approximately 1.5 cases per million persons per year. In all these studies it was assumed that the risk would persist for the rest of the lives of the exposed persons. On this basis the figure used by the United Nations Scientific Committee leads to the conclusion that the observed geographical differences in the average marrow dose from background radiation—of the order of 10 to 20 m.rad per year—would be unlikely to have produced much more than 5 to 10 cases per million persons in a 10-year period.

Further experience, however, has shown that the risk of developing leukaemia after irradiation is likely to diminish sharply after about five to eight years, though it has not yet been shown to disappear entirely. It therefore seems likely that a more realistic estimate would be that a dose of 1 rad to the bone-marrow might result in the production of about one case of leukaemia per million man-years for perhaps 10 years from the date of exposure (Court Brown and Doll, 1960). On this basis the observed differences in bone-marrow dose would be unlikely to produce more than 1 or 2 cases per million persons in 10 years. In contrast, the difference between Aberdeen and Dundee in the mortality from acute leukaemia and chronic myeloid leukaemia in a similar period is calculated to have been of the order of 170 cases per million persons and the difference between Aberdeen and Edinburgh to have been of the order of 130 cases per million persons. In our opinion, therefore, the finding of an excess mortality in Aberdeen from the two types of leukaemia that are known to be produced by radiation cannot be attributed to the high level of the background radiation. Knowledge of the mechanism of carcinogenesis is, however, incomplete, and the possibility that the effect of low doses of radiation has been underestimated should be borne in mind until more data are obtained.

Another source of radiation exposure is in the use of radiotherapy for medical diagnosis. Data collected by the Medical Research Council (1956) suggested that the average dose to the gonads from this source might be about 20–25% of that received from background radiation. Data for the average marrow dose and for its variation between different parts of the country are now being collected by the Committee on Radiological Hazards to Patients appointed by the Ministry of Health and the Department of Health for Scotland. No data are yet available, but it would not be surprising if the average marrow dose proved to be of the same order as that received from background radiation (United Nations, 1958). Since the dose-rate for diagnostic radiography is of the same order as that used in radiotherapy, there is less difficulty in attributing to it a leukaemogenic effect. Regional differences are, however, unlikely to be great, and it would be unreasonable to suppose that they could account for much more than the maximum effect estimated for the differences in background radiation.

Summary and Conclusions

Estimates have been made of the mortality from leukaemia for 10 parts of Scotland over the years 1939 to 1956. The highest mortality (146% of the expected) was recorded in Aberdeen, the second highest (124% of the expected) in Edinburgh, and the lowest (87% of the expected) in Glasgow. The mortality in Aberdeen was the highest recorded among men and among women; it was the highest recorded in the period 1947–56, but in the period 1939–46 (when the estimates are less reliable because of wartime movements of population) it was the second highest.

Estimates of the mortality attributed to acute leukaemia, chronic myeloid leukaemia, and chronic lymphatic leukaemia show that the excess mortality in Aberdeen was principally due to a high mortality from the two former types, while the excess in Edinburgh was principally due to a high mortality from chronic lymphatic leukaemia.

The excess in Aberdeen and Edinburgh cannot reasonably be attributed to random fluctuation. Possible explanations include (1) better case-finding, (2) high economic status, and (3) exposure to ionizing radiations.

It is suggested that better case-finding and a high economic status could account for the excess in Edinburgh and that better case-finding could account for some of the excess in Aberdeen. There are, however, reasons for thinking that this is not the sole explanation.

Measurement of the amount of radiation received from background sources were made in four areas—Aberdeen, Aberdeenshire, Dundee and Edinburgh. Estimates of the average marrow dose received from these sources indicate that the highest dose (101 m.rad/year, is received in Aberdeen and the lowest (80 m.rad/year) is received in Edinburgh. Extrapolation from the effects of large doses given at very much greater intensities suggests that differences of this order are unlikely to account for much more than 1% of the observed differences in mortality—if they are capable of being leukaemogenic at all.

Local differences in the average exposure to diagnostic radiography may be greater than the differences in background radiation. They may contribute to the variation in leukaemia mortality, but are unlikely to be a major factor in its production.

Whether the assumptions made in the present study are justified will not be apparent until further data are available. It is, however, clear that it is insufficient to study leukaemia mortality only in relation to background radiations. The proper interpretation of geographical variations can be made only when the effect of social and economic factors can also be assessed.

We are grateful to the Registrar-General of Scotland for the detailed data relating to leukaemia deaths and for the estimates of population by area in 1956; and to Dr. G. G. Dickie, Dr. I. A. G. MacQueen, Dr. H. E. Seiler, and Dr. I. B. L. Weir, Medical Officers of Health for Aberdeenshire, Aberdeen, Edinburgh, and Dundee, and to their staffs for facilities for making the radiation measurements and for their invaluable practical assistance. We are grateful to Dr. J. R. Greening, of the Department of Medical Physics, Edinburgh University, to Dr. C. A. Murison, Physicist to the Western General Hospital, Edinburgh, to Mrs. H. D. Griffith, Dr. D. Lindsay, and Mr. Low, of the Department of Medical Physics, Aberdeen University, and to Mr. McKie and Mr. Ritchie, of the Physics Department, Dundee Royal Infirmary, for assistance in making the radiation measurements; and to the Civil Defence Authorities in the areas studied for assistance in the selection of houses for examination. We are indebted also to Miss F. Callaby and Miss A. Fotheringham, of the Medical Research Council's Clinical Effects of Radiation Research Unit, for help in the collection of the data and in the analysis of the results.

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A new British Standard (B.S. 3232:1960) has been published dealing with the mechanical and electrical safety and the construction of medical treatment lamps for use in hospitals and the home. Copies may be obtained from the British Standards Institution, Sales Branch, 2, Park Street, London, W.1. (Price 5s., postage extra to non-subscribers.)

A SURVEY OF LEUKAEMIA IN CORNWALL, 1948–1959

BY

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Dameshek and Gunz (1958), discussing the incidence of leukaemia, remark that "statistical data available at present are fragmentary and too incomplete to permit definite conclusions about the prevalence of leukaemia. There is, moreover, *no* evidence so far that could show conclusively that the rate of leukaemia has actually risen."

They cite three sources of information available: (1) hospital series, (2) analysis of death certificates, and (3) special investigations to study the morbidity—and say it is not permissible to deduce the true incidence of leukaemia from hospital data, for many factors enter into admission to hospitals. At present the incidence of leukaemia is usually deduced from the mortality figures of the Registrar-General, and in general these figures lack the information necessary for accurate classification. The assumption is made that leukaemia is a lethal disease and therefore the death-rate must be an accurate reflection of its prevalence. That this is true of chronic leukaemia may be accepted, and reference to older textbooks gives a clear picture of the natural history of the disease. But in acute leukaemia the situation is different. Tidy (1954) refers to acute leukaemia as occurring under the age of 20 and most frequently in young children, and he makes no reference at all to the acute form as it arises in old people.

It is my experience that older practitioners brought up on similar teaching do not recognize acute leukaemia except among the young. Dameshek and Gunz say that it is "at least possible that the disproportionate rise in leukaemia mortality in the older age-groups represents the 'leeway' which has to be made up before there are comparable diagnostic facilities for all ages and with them comparable numbers of diagnoses of leukaemia."

The striking tendency of leukaemia to occur in old people was demonstrated over a large series of cases by Gunz and Hough (1956). In 553 cases of their own they found 57% over the age of 50. (Acute cases comprised 60% of these, and 46% of them were over the age of 50.) In Gunz and Hough's experience in New Zealand the assumption that manifestations of the disease remain the same at whatever age it occurs is not justified, and they believe that leukaemia presents a more insidious and less easily recognizable onset in old people.

It seems, therefore, that indisputable evidence is still required to show whether the rapid rise in the annual incidence which has been claimed by many workers during the last two decades is actual or only apparent. It is most important to know whether a steady annual rise can be observed and whether such an increase, if it occurs, does so in all age-groups or only in the elderly. It appears that the West Cornwall clinical area, in spite of its small size, provides an ideal locus for a study of leukaemia as it is arising to-day.

Only those who have worked in rural areas over the past 10 to 15 years know how greatly the scene has changed in respect of medical diagnostic facilities. Before 1945 there were few laboratories serving practitioners in rural areas; and it may be of value to describe the situation as it existed in Cornwall, because this is probably representative of the situation in rural areas elsewhere. Previous to 1936 there was no laboratory service at all; after the war the service grew rapidly, but blood counts still had to be paid for. In elementary form they were available for the well-to-do patients, but it is most unlikely that any haematological investigations were carried out on old or impecunious people whose anaemia was not gross and who could be accounted for as dying of heart failure or pneumonia. Chronic leukaemia was generally recognized, but the acute form, as an elusive, difficult-to-diagnose disease of the aged, was unknown. After "the appointed day" laboratories were increasingly thrown open and facilities for diagnosis became available for general practitioners. The first marrow puncture to be performed in Cornwall took place in 1946, when a case of acute aleukaemic leukaemia was diagnosed.

It is therefore apparent that no figures for leukaemia in Cornwall are even worth considering before 1948. The incidence of the disease after this date has been closely watched, and if the numbers are small it is at least believed that they provide an accurate cross-section of the disease as it has occurred in a rural area over the past 12 years.

Background

During the years 1948–52 it was noticed that the incidence of acute leukaemia was unexpectedly high in the central part of Cornwall, though for the county as a whole the incidence was about the same as that of the rest of England (0.5 per 10,000), and this localized increase was thought worth investigating.

Only the West Cornwall clinical area, which comprises that two-thirds of the county west of Liskeard, has been included in the survey, because patients from the eastern part of the county are generally referred to Plymouth.

Cornwall, in both its geography and its geology, presents features which may be important in surveying a disease suspected of an unusual distribution; it is a peninsula, almost separated from the mainland by moorland and by the Tamar river; the population was almost completely isolated in the past, and even to-day tends to remain within the county. It should be possible to study leukaemia here in people who have lived their whole lives in the same district and among the same surroundings as their parents and grandparents before them and to consider the disease in relation to the land on which they live.

Hewitt (1955) has called attention to a gradient in leukaemia mortality from a low level in the north of England to a higher level in the south, but very few records of a topographical nature have appeared in the literature on leukaemia. Clemmesen *et al.* (1952) examined the topographical distribution of leukaemia and Hodgkin's disease in Denmark over the period 1942–6, and these cases were plotted on a map but showed no significant pattern. Gauld *et al.* (1953) reported on the disease in the east of Scotland and found a predominance of the lymphatic type compared with most other published reports, but he was reporting on a hospital population. MacMahon and Clark (1956) have reviewed the disease as it appears in the Borough of Brooklyn, but it seems that no field survey of individual cases such as this has been made.

There is little doubt that leukaemia can under certain circumstances follow irradiation (Medical Research Council, 1956). It is known that local levels of radioactivity are high in Cornwall, and through the kindness of Dr. E. J. B. Willey a radiometric survey of the county was made and the relationship of irradiation to the geographical site of the cases compared. Though isolated pockets of high radioactivity occur, particularly on the granite areas of moorland, no obvious relationship with leukaemia could be found. St. Ives, a town with the highest local level of radioactivity, has a particularly low incidence, and this when part of the town's water supply is derived from an old uranium mine.

Geographical Distribution

It is convenient to divide the West Cornwall clinical area into two halves, providing two areas of equal population (approximately 116,000) for comparison. In the extreme west there were 81 cases, in the centre 130.

TABLE I.—*Leukaemia Morbidity in West Cornwall Clinical Area (Population 254,700), 1948–1959. Morbidity Rate per 100,000 West Cornwall Clinical Area=8.2 per 100,000 (11 Cases Surviving)*

District	Population	Incidence	Incidence per Annum per 100,000 Population
Bodmin	6,300	5	6·6
Camborne-Redruth	35,410	26	6·1
Falmouth	16,490	22	11·1
Fowey	2,320	8	28·8
Helston	5,830	4	5·7
Lostwithiel	2,020	1	4·1
Newquay	10,020	17	13·9
Padstow	2,890	2	5·8
Penzance	19,980	21	8·7
St. Austell	23,490	16	5·7
St. Ives	8,350	3	2·8
St. Just	4,020	7	14·5
Truro City	13,420	11	6·8
Truro R.D.	26,760	26	8·1
Kerrier R.D.	22,000	7	2·7
St. Austell R.D.	21,800	14	5·4
Wadebridge R.D.	15,860	5	2·6
West Penwith R.D.	17,540	16	7·6

As this difference between the two halves was more remarkable at the outset of the survey but has persisted to a less extent with improved diagnostic facilities, it is worth reporting. Table I shows the distribution of cases in the local authority areas.

Leukaemia is particularly uncommon in children in the western half, only two cases being recorded in 12 years; it is unlikely that the disease would be missed in a child, and so this deficit in a population of 116,000 is of interest. Three towns in the whole area show an incidence notably above the average; in Fowey 8 cases among 2,300 people seems excessive (one only of these was a short-time resident). In no rural district of comparable population was there any increase. In the larger towns the cases have been plotted on street maps, and, while coincidence can certainly not be ruled out, it appears worth recording cases which have been found living in close proximity. In one bakery two occurred within a few months—one acute myeloid, the other chronic. In each of two isolated villages two cases occurred in the same street and within a few yards of each other. In the town of 10,000 inhabitants (17 cases) where chronic lymphatic leukaemia predominates and local levels of radioactivity are low, two cases have occurred in opposite houses in the same street and two cases of reticulosarcoma were diagnosed near by. Here, within a radius of a quarter of a mile, seven leukaemias have been diagnosed within the last 12 years. In Fowey, owing to its small area, the cases were necessarily living in close relation to each other. E. J. B. Willey (1960, personal communication) has studied the radiometric aspects of these cases, visiting the patients' houses, and has found that the readings were uniformly low.

Clinical Study of Leukaemia in Cornwall

In 12 years 211 (115 acute) cases of leukaemia have been observed, and recorded according to age, type, and situation. Table II shows the number of cases diagnosed each year, with division into types. Table III shows that 25% of the patients are under the age of 40 and 75% over this age. The maximum numbers occurred in the 60–70 age-group, but in considering the numbers in extreme old age the population at risk has to be considered; the chance of acquiring the disease is gradually increased, and is obviously related to an increasingly aged population. It may be that people are surviving long enough to develop the disease. It is interesting that the rate per 100,000 of the population (Table IV) is almost identical in acute myeloid and chronic lymphatic leukaemia over the age of 70.

In 1948 eight cases of severe anaemia were referred for investigation and proved to be acute leukaemias. These, which would have been unrecognized before the day of marrow biopsy, raised the annual acute incidence considerably in that year, and it was not till 1952 that so high a level was reached again. There is therefore

TABLE II.—*Annual Incidence of Leukaemia According to Type*

Year	Myeloid, Acute		Lymphatic, Acute		Myeloid, Chronic		Lymphatic, Chronic		Total
	Male	Female	Male	Female	Male	Female	Male	Female	
1948	3	5	0	1	4	1	3	2	19
1949	3	4	0	0	2	3	0	1	13
1950	2	1	0	1	1	3	2	5	15
1951	2	2	3	0	1	4	1	0	13
1952	4	3	2	4	1	2	0	2	18
1953	9	2	3	0	0	0	5	1	20
1954	4	6	1	1	4	4	2	1	23
1955	4	2	0	2	0	1	4	0	13
1956	3	3	2	4	2	3	1	0	18
1957	3	1	1	1	3	0	2	3	14
1958	3	2	3	1	4	2	2	3	20
1959	7	5	1	1	1	3	3	4	25
Total	47	36	16	16	23	26	25	22	211

Acute Leukaemia—Mean Age of Onset in Four-year Groups:

1948–1951	1952–1955	1956–1959
27 years	46 years	60 years

TABLE III.—*Incidence of Leukaemia According to Age and Type*

Age-group	Myeloid, Acute		Lymphatic, Acute		Myeloid, Chronic		Lymphatic, Chronic		Total
	Male	Female	Male	Female	Male	Female	Male	Female	
0–5	2	1	6	4	0	0	0	1	14
6–10	4	0	2	0	0	0	0	0	6
11–20	3	3	0	1	0	0	0	0	7
21–30	4	4	1	1	0	0	0	0	10
31–40	2	4	2	2	2	2	0	1	15
41–50	6	3	0	0	2	6	1	1	19
51–60	5	11	1	3	1	5	4	4	34
61–70	10	4	1	3	11	6	7	9	51
71–80	9	5	2	2	6	5	10	5	44
Over 80	2	1	1	0	1	2	3	1	11
Total	47	36	16	16	23	26	25	22	211

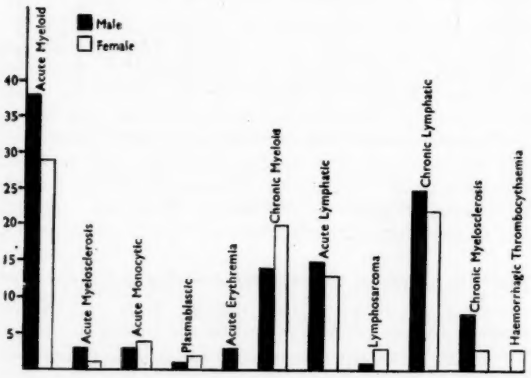
TABLE IV.—*Incidence of Leukaemia (Rate per 100,000) According to Age*

Age-group	Myeloid, Acute		Lymphatic, Acute		Myeloid, Chronic		Lymphatic, Chronic	
	Male	Female	Male	Female	Male	Female	Male	Female
0–5	15	8	45	31	0	0	0	8
5–10	34	0	17	0	0	0	0	0
11–20	12	14	0	5	0	0	0	0
21–30	17	17	4	4	0	0	0	0
31–40	9	17	9	8	9	8	0	4
41–50	26	12	0	0	8	23	4	4
51–60	25	45	5	12	5	21	20	17
61–70	65	19	7	15	72	29	45	44
71–80	96	38	21	15	64	41	106	38
Over 80	77	21	38	0	38	42	64	21

no evidence whatever in these figures that the incidence of leukaemia has increased over the last 12 years. There is reason to suppose that there may have been a diagnostic deficit from 1949 to 1951 ; but 1955 and 1957 seem to have been years of genuinely low incidence. The average number of leukaemias in West Cornwall is between 17 and 18 per annum in a population of approximately 254,000, or about 0.6 per 10,000.

Leukaemias classed as acute have had a life-history of less than a year after the onset, but it is often difficult to be sure how long some sort of ill-health preceded the moment of recognition. Typing of leukaemias is often difficult, and no great stress has been laid on this ; acute myeloid and monocytic cases, and acute cases with myelosclerosis, have all been grouped as myeloid in the tables. Three cases diagnosed as acute plasmablastic leukaemia from their unusual and primitive morphology and confirmed at necropsy have also been put in this group, together with one erythroleukaemia and two acute erythremias. Lymphatic leukaemias and lymphosarcomata with a leukaemic blood picture and generalized lymphoid infiltration of the tissues have been put together.

Among the chronic myeloid leukaemias, myelosclerosis and haemorrhagic thrombocythaemia have been included as being closely related. The Chart shows the distribution of all the types encountered.



Distribution of types of leukaemia encountered.

Incidence

Mean Age at Onset.—In chronic leukaemia the mean annual age at onset has remained much the same. In 1948 it was 60, and in 1959 it was still 60 years. There was a fluctuation between 56 years in 1950 and 74 in 1958. In the acute leukaemias a very different picture emerges (Table II). In 1948 the mean age at onset was only 19 years, but it has steadily risen since, remaining round about 30 until 1953, when it rose abruptly to 61, and in 1957 reached a peak at 69. The mean age was reduced in 1956 and in 1959 by the occurrence of two leukaemias in children. Taken over the whole period this is a startling rise, reflecting the absence of leukaemia in young people in Cornwall.

Leukaemia in Childhood.—Up to 1954 two or three cases occurred annually in young children. Since then only two—one in a baby, the other in a boy of 9—have been discovered.

In other surveys (Hewitt, 1955) the peak incidence has been found at 3 years of age and in boys ; here this peak (four out of six under 5 years) appears in girls but not in boys. The numbers are, however, too small to be statistically significant. They do, however, show that there is no evidence of an increase of leukaemia among children in Cornwall, and it may be that there is an actual fall. This finding, for what it is worth, is encouraging and would account for the fact that there is no annual increase in cases in spite of the absolute increase in incidence among old people.

Incidence in Relation to Retirement Age and Short Residence.—It may be objected that there is an undue proportion of retired people in some of these Cornish towns and that they tend to overweigh the numbers at risk in the population. Thirteen patients over the age of 55 had retired here, though all except three had been living here for five years, and some for a considerable time. This gives a non-Cornish element of retired people of 6% to be taken into consideration—but it has little effect on distribution except in Fowey, where the number might be reduced by two. If retirement is a factor, the highest figures would be expected in such towns as St. Ives, Falmouth, Penzance, and Fowey. Seven other younger patients may have lived in the county for less than five years ; among these was a child whose parents were temporary residents. The short-term total is therefore not more than 10%. Visitors have been excluded from the survey.

Sex Incidence.—In common with other surveys a predominance of males has been most pronounced up to the age of 10. It does seem that women are more prone to develop leukaemia during the fifties and men to develop it later in life. Acute myeloid leukaemia shows a predisposition towards males, but chronic lymphatic leukaemia, usually predominant in males, does not show this tendency to any great extent in Cornwall.

Method of Diagnosis

Diagnosis was made by marrow puncture in 88 acute and 27 chronic cases. It was confirmed by necropsy in 25, but it is often difficult to carry out post-mortem examinations on people dying in rural areas. In 21 cases confirmation by other haematologists was obtained, and in seven the diagnosis was made by biopsy. In 75 cases (39 acute and 36 chronic) the diagnosis was obvious from the clinical findings and the peripheral blood picture, and possibly this number (35% of the total) represents the hard core of incidence which would have been reported at any time in the last 25 years and in the absence of any special diagnostic facilities. It is interesting that rather more acute than chronic cases were diagnostically obvious, but the latter group includes 11 myeloscleroses requiring confirmatory investigation, three haemorrhagic thrombocythaemias,

and some chronic lymphatic leukaemias seen in the pre-leukaemic stage.

Onset of Leukaemia

To prove that the diagnosis of leukaemia, particularly in its acute forms, is often not immediately obvious, the first blood counts received from these patients were studied. In 52 (24%) a firm diagnosis would not have been possible from a blood count alone, at least when the patient was first seen, and it is surprising that 22 of these were chronic cases. A general practitioner suspecting anaemia may be reassured by the result of a single blood examination and fail to ask for a further investigation, and this is particularly true in the case of the very acute leukaemia where death may occur before the haemoglobin level has fallen significantly. The speed at which death can take place in an acute leukaemia must have rendered diagnosis in such a case virtually impossible in the past. On one occasion a general practitioner was called for the first time to see an old man *in extremis*. A blood film only was taken; this showed numerous blast cells, but the patient was already dead by the time the report was received. Five cases were recognized only at necropsy; two of them had defied definite diagnosis and two of the patients had died suddenly. Failure to examine the tissues histologically in three of these cases would have resulted in the diagnosis being missed.

The haemoglobin level at first appearance is remarkably high (Table V): 45 cases showed a haemoglobin over 10 g., and three were recorded at over 15 g.; 68 fell between 7.5 and 10 g., and none were seen with a haemoglobin level under 3 g.

TABLE V.—*Haematological Findings with Clinical Signs and Symptoms in 95 Cases of Acute Leukaemia*

Clinical Findings	% Incidence	Haemoglobin g./100 ml.	% Incidence	Leucocytes/c.mm.	% Incidence
Haemorrhages, including petechiae and bruising	45	15+	1	800,000+	2
		12–15	8	400–800,000	3
		10–12	9	300–400,000	4·5
Infections	36	8–10	18	200–300,000	4·5
Malaise and general ill-health	30	7–8	30	100–200,000	8·5
		5–7	14	50–100,000	13
Splenomegaly	24	4–5	12	20–50,000	18·5
Lymphadenopathy	16	3–4	8	10–20,000	13
Skin lesions	12			5–10,000	14
Loss of weight	11			1–5,000	17
				<1,000	2

In only 69 (50 acute) of these patients was the total white count over 20,000, and in 31 acute cases it was under 10,000.

Presenting Symptoms.—The history was known in 90 acute cases. A complaint of increasing fatigue was usual and indeed the only significant symptom in 24 cases, and it would seem that the appearance of a few petechiae, bleeding from a mucous membrane, or recent onset of bruising, combined with a moderate degree of anaemia, is the most common presentation of acute leukaemia. In 39 cases some form of sepsis occurred, such as boils or gum or tonsillar lesions, and three were referred direct from a dentist. A recent history of herpes labialis was found in seven cases personally investigated. Examples of atypical presentation were as follows: dermatoses, suspected ovarian cyst, agranulocytosis, thrombocytopenic purpura, pernicious anaemia, nutritional anaemia, and cases discovered on routine pre-surgical examination.

Past History.—In all cases seen after 1954 past illnesses, injuries, and *x*-ray status have been studied. Only 10 of the cases had been previously *x*-rayed; two of these had had intravenous pyelograms and two or three cholecystograms. Three had been to a mass *x*-ray unit. It seemed that a history of gall-stones was unduly common, but this may be discounted in that gall-stones are unduly common in Cornwall anyway. Thirteen patients had had pneumonia some time before the onset, and at least 20 dated the beginning of their illness at some febrile illness, usually called "flu." Skin lesions were associated with the onset in 10 cases. Once only was there a familial incidence, when a mother and son developed subacute lymphatic leukaemia within six months of each other. This compares with Guasch's (1954) incidence of 0.5%.

Prodromal Period in Acute Leukaemia.—In 57 cases it was possible to assess the time interval between the patient's first complaint and the diagnosis of the fully developed disease. In 11 cases it was 14 days or less, in 20 between two and six weeks, in 20 between two and six months, and in 6 there had been complaints of ill-health for two to three years. Six were seen in the pre-leukaemic stage, and a firm diagnosis was possible only after several months.

Radiology and Leukaemia

Following the work of Stewart *et al.* (1956) an inquiry into the *x*-ray status of the mothers of the leukaemic children was made. At the West Cornwall Hospital between 1942 and 1950, 391 pregnant women had abdominal radiographs; in addition there were 122 pelvimetries. These investigations have now been reduced to one or two annually.

At the obstetric centre at Redruth a survey has been made of all pregnant women undergoing *x*-ray examination between 1948 and 1959. Records of 1,175 women were scrutinized and 200 pelvimetry estimations were noted. No mother of a leukaemic child has been found in either investigation. The mother of one leukaemic child had had an abdominal *x*-ray examination, not in the pregnancy but in a previous one, and that child is healthy.

Investigations into the *x*-ray status of the mothers of the 20 leukaemic children showed that one only, an elderly primipara, had had a straight abdominal *x*-ray examination in the 35th week of the pregnancy.

Economic Background

Witts (1957) refers to leukaemia as more common in the rich than in the poor, in whites than in non-whites; this can be explained, at least in part, on the grounds that previously only the well-to-do could afford or even obtain the investigations necessary for making the diagnosis of an acute aleukaemic leukaemia. Study of the economic background of our series does not show any marked economic gradient. In all there were 20 cases in social group 1. Half of these were not Cornish, and some were comparatively recent residents. Thus an average of less than 2 per annum, or 10%, hardly justifies belief in a high economic gradient. On the other hand, most of the patients were comfortably housed and well fed in the Cornish manner; many were small farmers and agricultural workers, and if good nutrition predisposes to this disease there is nothing here to contradict that.

Notification to the Registrar-General

Death-certificate notifications were compared with clinical diagnoses in the western half of the area. There was a discrepancy of at least 11%, but this was largely cancelled out by five false-positive and four false-negative notifications. This investigation needs to be done on a larger scale, but it does not seem that any significant revision would have to be made.

Discussion

There is no evidence here to show that the incidence of leukaemia has increased during the past 12 years in Cornwall, but there may be some evidence that it is becoming less frequent in the very young. This is in accordance with the opinion of Gilliam and Walker (1958), who said that "presently evident trends in death rates from leukaemia offer no support for a theory that leukaemogenic factors in the American environment have increased sharply within the last 15 years." The disease is now more often diagnosed among the aged, and the mean age at onset shows a steady rise during the period 1948–59. It is argued that this is due to an increasing awareness of acute leukaemia as a disease of old people. Better facilities for diagnosis have resulted in the more frequent discovery of acute leukaemia at all ages over 50, and these facilities first became operative about 1948.

Poverty seemed to have no part in the aetiology of the disease. Saxton *et al.* (1944) showed that underfeeding of mice reduced the incidence of spontaneous leukaemia from 65% to 10%, and Engelbreth-Holm (1954) says that the restriction of calorie intake reduces the incidence of other spontaneous tumours besides leukaemia. The appearance of leukaemia in the well-nourished in Cornwall seems to support the experimental evidence.

There is no significant evidence here that *x*-ray films taken during pregnancy have been associated with leukaemias developing in children. Nor is there any evidence that high local levels of radioactivity associated with granite outcrops in Cornwall have any influence on the disease.

It may be that the type of leukaemia shows a variation in different parts of the country (cf. East Coast of Scotland), and further surveys of this kind might add to our information.

Summary

A survey has been made in Cornwall to determine the pattern of leukaemia as it is occurring in a localized area with a static population, and also to decide whether there is any evidence of an absolute increase in its incidence.

The influences which determine accuracy of diagnosis have been considered; past failure to recognize leukaemia as a disease of the aged probably accounts for the increasing notification of cases among the elderly. Improved laboratory diagnostic facilities play a part in the increasing accuracy of diagnosis.

The geographical distribution of the cases has been studied; there is a tendency to find tiny foci of victims living in close proximity but no significant predominance in any particular district.

In spite of improved facilities no evidence of an increasing incidence has been found in Cornwall since 1948. The possibility that the disease is becoming less common in children is suggested.

There is, on the other hand, clear evidence that the average age incidence of reported cases has increased steadily over the period.

The economic background of the patients is good.

Possible influence of leukaemogens on the incidence has been studied with particular reference to local radiometric levels, which are high, and also to the irradiation of mothers during pregnancy. No significant relationship has been found.

The accuracy of notification of the disease to the Registrar-General has been investigated in a small population and has been found to be reasonably accurate, but there is no means of knowing how often the diagnosis of acute leukaemia has been missed in the past.

My thanks are due to Mr. J. W. Walker, chief technician at the West Cornwall Hospital, for tireless assistance in a laborious work; to Dr. E. J. B. Willey, who spent countless hours making a radiometric survey of Cornwall; to the staff of the *x*-ray department of the Camborne-Redruth and Penzance Hospitals for producing large numbers of records; to Dr. E. R. Hargreaves and his staff at County Hall, Truro, for much help; to Dr. W. R. S. Doll, of the Medical Research Council Statistical Unit, for criticism and advice; and to all the doctors, too numerous to mention, who kindly reported their cases of leukaemia to me. The expenses were defrayed by the Research Committee of the South-western Regional Hospital Board.

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World Health Day this year was devoted to malaria and to the world-wide campaign to eradicate the disease from which Great Britain herself only began to be free about 100 years ago. The Venerable Bede's *Historia* records a case in the Fens district as early as the seventh century, and a tertian ague was said to have killed James I in 1625 and Oliver Cromwell in 1658, and to have attacked Charles II. That there was malaria in Kent and Essex was common knowledge in Charles Dickens's day: Pip in *Great Expectations* says to the shivering convict: "You've been lying out on the meshes, and they're dreadful aguish." Other marshy areas in which agues were common were the Cambridgeshire and Lincolnshire Fens, the marshes of the Thames Estuary, of Romney and Pevensey, and of Bridgewater near the Bristol channel. In 1850 and 1860 between 12 and 60 per 1,000 admissions at St. Thomas's Hospital were for ague. In 1862 the building of the Thames Embankment meant draining and reclaiming land at the river margin, and by 1864 the disease was rapidly disappearing after at least twelve centuries. (From Dr. Harold Scott's *History of Tropical Medicine*.)

BELL'S PALSY: SOME PROBLEMS OF PROGNOSIS AND TREATMENT

BY

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This study is based on a survey of the patients suffering from facial paralysis examined by me in the E.N.T. department of the United Birmingham Hospitals during a two-year period 1954 to 1956.

The aims of the investigation were to seek criteria which will give guidance on the probability of spontaneous recovery in idiopathic facial paralysis and to assess the value of present methods of treatment.

Material and Methods

Of the 107 patients (54 male, 53 female) examined, 56 were affected on the right, 49 on the left, and 2 bilaterally. Their ages ranged from 5 to 75 years, the highest incidence being in the 30–40 age-group. All the palsies were of lower-motor-neurone type, and so in a sense could be described as cases of Bell's palsy; for in 1821 Bell distinguished between "paralysis which proceeds from the brain, and that affection of the muscles of the face when from a less alarming cause they have lost the controlling influence of the respiratory (i.e., facial) nerve." However, the term Bell's palsy is nowadays reserved for those cases of peripheral facial palsy in which there is no obvious cause such as injury, infection, or new growth (Cawthorne, 1951).

Preliminary investigations established pathological causes in 10 patients. They were: (*a*) chronic mastoid infection (three patients); (*b*) intratemporal epidermoid of the type described by Jefferson and Smalley (1938) (two patients); (*c*) fracture involving the temporal bone (two patients); (*d*) sarcoidosis (one patient with bilateral paralysis); (*e*) acute middle-ear infection (one patient); (*f*) brain-stem glioma, which presented originally as a nuclear lesion (one patient). These are listed for completeness and are not discussed further.

Bell's Palsy and Ramsay Hunt's Syndrome

The remaining 97 patients are considered as a group. One of the 97 returned with a palsy on the opposite side nine months after her first attack, so 98 cases are available for consideration

It might be expected that they would comprise, on the one hand, the idiopathic affection called Bell's palsy and, on the other, the facial paralysis associated with herpes zoster affecting the head or neck, and often with auditory-nerve symptoms, described by Ramsay Hunt (1907).

Collier (1951, 1954) pointed out that Bell's palsy is probably a condition of multiple aetiology, some cases being due to exposure to cold, while others occur in small epidemics, sometimes associated with epidemics of herpes zoster and of anterior poliomyelitis.

In the present series eight patients attributed the condition to exposure to cold, two to recent childbirth, and two to dental extractions. Two patients told of another member of the household who had a transient facial paralysis; in one of these instances the children of the house were recovering from chicken-pox at the time.

Aitken and Brain (1933) showed by a complement-fixation test the presence of a zoster antibody in the serum of each of nine cases of Ramsay Hunt's syndrome; they then proceeded to demonstrate the antibody in the serum of 4 out of 22 cases of Bell's palsy. These four were indistinguishable clinically from the 18 in which the reaction was negative.

I have therefore regarded those cases of Ramsay Hunt's syndrome in the present series as simply more florid cases of Bell's palsy, bearing in mind that the latter term embraces a variety of conditions, some of which may be due to a zoster infection.

Investigations

A careful history was taken in each case and the completeness or otherwise of the paralysis assessed visually. Otological and neurological examinations were carried out; in many cases radiography of the mastoids, audiometry, and caloric tests of labyrinthine function were performed.

An attempt was made in each case to test the function of the three branches of the nerve which arise within the temporal bone. They are the chorda tympani, the nerve to the stapedius, and the greater superficial petrosal nerve.

The *chorda tympani*, the most peripheral branch, arises 4–6 mm. above the stylomastoid foramen. It conveys secretomotor fibres to the submandibular and sublingual glands, and taste fibres from the anterior two-thirds of the ipsilateral half of the tongue. The cell bodies of these afferent fibres lie in the geniculate ganglion of the facial nerve in the medial wall of the attic of the middle ear. No attempt was made to investigate the secretomotor function, and the gustatory function was assessed by electrical testing, using a galvanic current. An indifferent electrode having been attached to one arm, the circuit is completed by a metal electrode applied to the tongue. The current strength it slowly increased until the patient indicates that he is aware of the current, and the threshold recorded in milliamperes. In this way the threshold is recorded for various parts of the tongue. It is found that in normal individuals this threshold is rarely higher than 1.5 mA and usually below 1 mA, while in patients in whom the chorda tympani is known to have been divided in radical mastoid operations (but in whom the "common sensation" due to the mandibular nerve is intact), the threshold is much higher, usually in the order of 4 mA. Nearly all patients with a known or suspected chorda lesion have commented on the difference between the metallic taste on the sound side of the tongue and the sensation of an electric shock on the affected side.

This test is a variation of that described by Mackenzie (1955), who applied both electrodes to the tongue, and similar to that of Krarup (1958). It appears to be a valid method, for the same result could be obtained repeatedly in the same patient, and in those with a taste-defect the area of hyposensitivity corresponded accurately with the anatomical distribution of the chorda tympani.

It is interesting that while some patients noticed an absence or alteration of taste on the affected side at the onset of the paralysis, the majority in whom a chorda lesion (from any cause) was demonstrated were unaware of any loss of taste.

The *nerve to the stapedius* arises above the chorda tympani in the vertical portion of the facial nerve. The stapedius exerts a protective damping effect upon sound vibrations reaching the inner ear and is activated reflexly

by sounds of fairly high intensity (Hallpike, 1935). Patients were questioned about their reactions to loud sounds, and some gave a clear-cut history that such sounds as children's voices and clashing crockery were almost intolerable during the early stages of the paralysis.

The *greater superficial petrosal nerve* arises at the level of the geniculate ganglion. It supplies secretomotor fibres to the lacrimal gland and conveys taste from the soft palate via fibres which, like those of the chorda tympani, have their cell bodies in the geniculate ganglion. (1) The rate of secretion of the lacrimal gland was studied by Schirmer's (1903) test, in which a strip of filter paper is hooked over the lower lid to act as a wick, and the rate of flow along it compared with that along a similar strip applied to the opposite eye. The test proved rather difficult to apply, owing to the fact that in facial palsy the lower punctum tends to sag away from the globe, causing the eye to "water." In fact, in only two cases was unequivocal hyposecretion observed on the same side as the facial paralysis. (2) The taste on the soft palate has been investigated as on the tongue.

Strength–duration curves were plotted in most cases in which the paralysis persisted for four weeks or longer, and electromyography was carried out in three patients. These tests are referred to later.

Prognosis

Associated Symptoms

It is widely held that the severity of associated symptoms, especially pain, at the onset worsen the prognosis for complete recovery of facial function (Tumarkin, 1936; Sullivan and McAskile, 1952; Cawthorne, 1952; Kettel, 1959). Therefore in the present series a clinical classification has been adopted according to the presence of symptoms, apart from those due to a lesion of the facial nerve itself (for example, loss of taste). Four groups have been distinguished. Group A: facial paralysis, herpetic vesicles, eighth nerve symptoms, and pain—that is, Ramsay Hunt's syndrome. Group B: facial paralysis, eighth nerve symptoms, and pain. Group C: facial paralysis and pain. Group D: facial paralysis only.

Group A.—Seven patients presented a complete facial paralysis, eighth-nerve symptoms, and herpetic vesicles, affecting the distribution of one or more cranial or cervical nerves, and associated with severe pain. Ramsay Hunt postulated the existence of a sensory area of distribution of the facial nerve, this area being the external auditory meatus and the external surface of the concha. He regarded this nerve supply as being superimposed on the generally accepted nerve supply to the region, by the auriculo-temporal, auricular branch of the vagus, and greater auricular nerves. Herpetic eruptions were seen in the area he described in five cases, while in the other two the tongue and palate were affected. All seven suffered from aural vertigo, three from perceptive deafness, and one from a recurrent laryngeal-nerve palsy. Two patients made a complete recovery—one in five weeks and one in seven weeks from the onset; four had made a partial recovery within 12 months; and one showed no recovery at all in that time.

Group B.—Five cases have been placed under this heading because they had auditory-nerve symptoms and severe pain, in addition to a complete facial paralysis. They would seem to represent a clinical halfway stage between Bell's palsy and Ramsay Hunt's syndrome. Four had vertigo, and two perceptive deafness with tinnitus. One patient was admitted for lumbar puncture because of slight nuchal rigidity. The C.S.F. contained 131 cells/c.mm., of which 98% were monocytes. Two patients had recovered complete facial function at 4 and 16 weeks from the onset respectively, while the other three had a partial paralysis 12 months after the onset.

Group C.—The patients whose only other complaint was pain at the onset of the paralysis numbered 44, of whom 36 had a complete and 8 an incomplete paralysis. The description varied from a dull ache to excruciating pain, and the duration of the pain from a few hours to two weeks. Some patients had multiple sites of pain and in several the distribution of a cutaneous nerve was defined accurately. The frequency of the sites mentioned were: external auditory meatus, 16; mastoid process, 13; neck, 11; mandible, 5; occiput, 4; maxilla, 2; auriculotemporal nerve, 1; ophthalmic nerve, 1. In every case the pain was limited to the same side of the head and neck as the facial paralysis. Five patients did not return for re-examination. One-third of those who were followed up (13 out of 39) achieved partial recovery within a year and 26 made a complete recovery.

Group D.—42 patients presented with facial paralysis and no other symptoms or signs (except those due to a lesion of a branch of the facial nerve); 23 had a complete palsy, while 19 retained some function of the nerve throughout. Five patients also did not reattend after the first examination. Less than one-sixth of those who were followed up achieved only partial recovery within a year, while 31 out of 37 made a complete recovery.

The recovery rates in the four groups are shown in Table I. While the numbers in groups A and B are small, the overall pattern of Table I confirms that the probability of complete recovery is lessened by the presence of pain at the onset, and is much diminished by the presence of auditory-nerve symptoms and herpes. It should be noted, however, that of the 12 cases in groups A and B four made a complete recovery, three of them within seven weeks of the onset.

TABLE I.—*Associated Symptoms and Recovery Rate*

Group	No. of Patients	Paralysis Complete	Recovery			
			Complete	Partial	None	Not Known
A	7	7	2	4	1	0
B	5	5	2	3	0	0
C	44	36 (82%)	26 (59%)	13 (30%)	0	5 (11%)
D	42	23 (55%)	31 (74%)	6 (14%)	0	5 (12%)

Branch Lesions

One of the aims of this investigation was to discover whether the presence or absence of lesions of the intratemporal branches of the facial nerve would offer a guide to prognosis. In Table II the recovery of the 88 patients who continued to attend is analysed according to the branch lesions discovered at the first examination. It is clear that in this series the ultimate result bore no relation to the presence or absence of taste-loss or intolerance of loud sounds. The fact that both patients with a "dry eye" failed to make a complete recovery may, however, be significant.

Incomplete Paralysis

The impression that when the initial paralysis is incomplete complete recovery can be expected was confirmed in this study, for 22 patients whose paralysis

TABLE II.—*Relation of Intratemporal Branch Lesions to Ultimate Recovery of Facial Nerve*

Branch	Function	No.	Recovery		
			Complete	Partial	None
Chorda tympani	Lost	44	30	13	1
	Retained	44	31	13	—
Nerve to stapedius	Intolerance of loud sounds	8	8	—	—
	No intolerance	80	53	26	1
Greater superficial petrosal: Taste on palate	Lost	9	7	2	—
	Retained	79	54	24	1
Lacrimation	Diminished	2	—	2	—
	Not diminished	86	61	24	1

was never complete continued to attend, and all made a complete recovery.

Duration of Paralysis

It is well known that the longer the interval between the onset of paralysis and beginning of recovery the less likely is complete recovery to occur. Of 61 patients who achieved complete recovery, 59 had visible voluntary movements within 6 weeks, one in 8 weeks, and one in 12 weeks; while of 26 patients who achieved only partial recovery, one showed some improvement in 3½ weeks, one in 4 weeks, two in 7 weeks, and 21 at intervals of from 9 weeks to 6 months from the onset. Cawthorne (1951) found that if recovery was going to be complete it usually started within a month of the onset.

Recurrent Cases

In this series, five patients gave a history of more than one attack of facial paralysis. Four had experienced a previous attack on the opposite side and one on the same side. One patient, a woman of 47, was observed during both attacks. In August, 1955, she had a complete right-sided facial paralysis with severe mastoid pain. There were no branch lesions. Voluntary movements did not return for three months, though strength–duration curves and electromyography suggested that denervation was incomplete. Recovery was slow and incomplete, with marked synkinesia. In May, 1956, she reattended with a complete facial paralysis on the opposite side. There was no pain, but taste was absent on the same side of the tongue. Recovery began on this side in three days and was complete in eight weeks. The evidence of this case thus supports my view that the presence of pain is of more prognostic significance than is a lesion of a branch of the nerve, such as loss of taste.

Pathology

The facial nerve and its connective-tissue sheath traverse a rigid canal, which is 30 mm. long, within the temporal bone. Many authors, including Ballance and Duel (1932), Morris (1938), Cawthorne (1946), and Kettel (1947), who have operated on the facial canal in cases of Bell's palsy, have described how, in many cases, the nerve is under tension and bulges when the sheath is slit after the canal has been opened, especially in the lower part of the vertical portion of the canal, where the sheath is thickest.

It is believed (Blunt, 1956; Kettel, 1947, 1959) that this oedema of the nerve is due to a dysregulation of the circulation within the facial canal. They postulate that ischaemia of the nerve due to a primary arteriolar vasoconstriction near the stylomastoid foramen leads to oedema and secondary ischaemia. Blunt concedes that an initial swelling of the nerve due to some cause other than primary ischaemia might set up a vicious circle of compression, ischaemia, oedema, and further compression, but found no convincing evidence of such an initial neuritis.

Wyburn-Mason (1954) has produced evidence that some cases of Bell's palsy are due to a neuritis or irritative lesion of the second and third cervical nerves, and he suggests that in these cases the greater auricular nerve involves the facial nerve by way of the branches of communication between the two nerves in the region of the parotid gland.

Denny-Brown, Adams, and Fitzgerald (1944) reported necropsy findings on a case of Ramsay Hunt's syndrome. They found typical necrotizing ganglionitis of the second dorsal root ganglion, and, while the facial nerve was infiltrated with dense patches of lymphocytes, the geniculate ganglion was virtually normal.

Similar findings reported by Findlay (1950) and by Kettel *et al.*, 1959, led Kettel (1959) to agree with the conclusion of Denny-Brown *et al.* that the evidence for geniculate ganglionitis in Ramsay Hunt's syndrome is invalid.

Functional Block or Degeneration?

James and Russell (1951), in a series of 58 cases, drew attention to the fact that those who achieved complete recovery showed the first signs of improvement in two to four weeks, while in those in whom recovery was incomplete the return of voluntary movement was delayed for two to four months from the onset of the paralysis. The recoveries in the present series conform to the pattern of those of James and Russell, and it is over the treatment of the patients who start to recover later (and, as has been shown, incompletely) that considerable diversity of opinion exists.

In the larger group of patients who recover early it is believed that the nerve below the lesion is in a state of "physiological block" or neuropraxia—that is, it is capable of conducting impulses—and normal function is possible as soon as the lesion causing the block subsides. Neuropraxia may persist for several days or weeks before recovery or degeneration occurs.

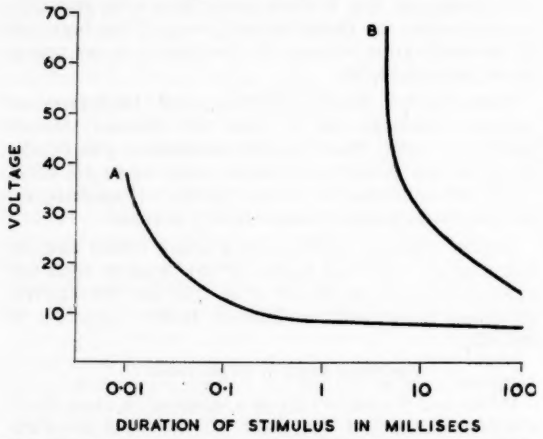
In the smaller group in whom delayed recovery occurs the nerve fibrils below the lesion are believed to have undergone degeneration. Recovery is then possible only when regenerating axons traverse the site of the lesion and follow the peripheral neurilemmal tubes to the muscle fibres. If the tubes are shrunken and distorted recovery will be imperfect; if axons enter the "wrong" tubes, synkinesia—associated movements of different parts of the face—will result; while if the lesion is proximal to the origin of the greater superficial petrosal nerve, lacrimation on eating may give rise to the annoying symptom of "crocodile tears."

The state of the nerve below the lesion may be assessed by the strength–duration curves, the faradic test, and electromyography. In the present series strength–duration curves were plotted in most cases in which clinical recovery had occurred in one month, and were repeated at monthly intervals. Electromyography was carried out on three patients only, and the faradic test as such was not used at all.

Electrodiagnosis

Strength–Duration Curves.—The time for which a given voltage must be applied over the "motor points"

of individual facial muscles to produce a contraction is determined, and the results are plotted for various voltages as in the Chart. If there is functional block but the nerve has not undergone degeneration a normal curve (A) is obtained. If degeneration has occurred the curve shows a shift to the right because denervated muscle which is being stimulated directly is less sensitive than muscle which is innervated.



Strength-duration curves. A=Normally innervated muscle. B=Denervated muscle.

Faradic Test.—It is evident from the Chart that electrical stimuli shorter than a certain critical duration will not activate denervated muscle, however strong the current may be; this is the basis of the faradic test, for in a faradic current the duration of the impulses is too short to excite denervated muscle but long enough to stimulate functioning nerve fibrils.

Electromyography.—Here an individual muscle is needled and the electrical disturbance on attempted contraction is recorded on a cathode-ray oscillograph. Spike potentials denote intact functioning nerve fibres even when no obvious movement is present. Fibrillation potentials indicate denervated muscle fibres which are capable of function if reinnervated.

These three methods of electrodiagnosis are not infallible. The strength-duration curve represents the curve for the most excitable fibre present, and may not take account of other less active or degenerate fibres. The electromyograph may show the presence of active motor units, but from the patients' point of view a sufficient number of motor units to produce an acceptable cosmetic result is the most important consideration.

Collier (1954) stressed that too much should not be expected of these electrical aids to diagnosis, but advocated their repeated use as a guide to progress.

Methods of Treatment

Treatment in the present series was by standard methods. Analgesics and bed-rest were advised when necessitated by pain and vertigo, and local treatment was directed initially to ensuring that as little harm as possible came to the paralysed muscles while the function of the nerve was in abeyance.

A rubber-covered wire splint, hooked into the angle of the mouth and looped over the pinna like a spectacle frame, was used to prevent overstretching of the muscles by the drag of the paralysed face. In prolonged cases an intraoral splint was fitted by dental colleagues to the upper teeth or denture for the same purpose.

Radiant heat was prescribed if pain was present. As soon as pain was absent galvanic stimulation was given daily to maintain the contractility of the muscles. Later the interval was lengthened to twice weekly.

When voluntary movements could be discerned active exercises were prescribed, care being taken that simultaneous movement of the sound side of the face was limited to a minimum to avoid overstretching of the muscles of the weak side.

All observers are agreed that 75 to 85% of cases make a full recovery under such a regime, which in effect consists of waiting for spontaneous recovery of the nerve. Korkis (1959) has shown that the percentage of early complete recoveries may be substantially increased by treating all patients in the early stages by cervical sympathetic blockage.

Authoritative opinion is divided on the value of surgical treatment in the 20% or so of patients who have not begun to recover within a few weeks of the onset, and the advocates of decompression are not entirely agreed on the indications for intervention.

To Decompress or Not?

As swelling of the nerve and compression by the rigid canal are a feature of Bell's palsy, surgical decompression seems at first sight to be a logical procedure, but Collier rightly insists that we should be clear about the object of the operation. Is it to prevent degeneration or to promote regeneration?

If it is to prevent degeneration the operation should be carried out in the early stages—when we know that 80% would have recovered completely and most of the remainder partially in any case. Even supposing that all patients with a complete paralysis were submitted to operation early, on the grounds that there is no means of selecting the unfortunate 20% who will not spontaneously recover completely, there is no evidence that more patients would get complete recovery. The available evidence on early decompression is in fact discouraging. Kettel (1947, 1959) described how he decompressed the nerve in the early stage of paralysis on five occasions. Operation was carried out after 12 hours, 7 days, 8 days, 8 days, and 12 days of complete paralysis in the five cases respectively, and only partial recovery was obtained in each. Kettel stated that in two cases the results were among the poorest he had had from decompression. It is difficult to resist the conclusion that, even in his very experienced hands, decompression was harmful in the early stages of paralysis. He has given as his indications for decompression, paralysis which is still complete after two months, recurrent paralysis, paralysis with severe pain, and cessation of spontaneous improvement short of complete recovery. He disregards the faradic test as an aid to prognosis.

Cawthorne (1951) has advocated decompression when complete paralysis has been present for a month and the faradic reaction is negative. He believes that while such cases are unlikely to obtain complete recovery, with or without operation, speedier and more complete recovery occurs after operation, and that troublesome spasms of the facial muscles are less likely to occur.

Sullivan (1952) has advised decompression if no recovery has occurred in six weeks, or earlier if complete

facial paralysis is accompanied by pain and loss of the faradic response.

Decompression in the Present Series

Decompression was carried out in four patients, each of whom had a complete paralysis. Complete recovery occurred in one, partial recovery in two, and no recovery in one.

Case 28.—A man of 42 suffered a complete paralysis with no pain or other symptoms. Electrical tests were not carried out. There was no improvement in eight weeks and decompression was performed. The nerve was found to be swollen. Five days later voluntary movements were present and recovery was complete within four months of the onset.

Case 86.—A woman of 28 with a right complete facial paralysis and mastoid pain was treated conservatively for two months without improvement. The strength–duration curves were to the right in one month and unchanged in two months. Electromyography showed fibrillation but no motor unit potentials. At operation the upper third of the vertical portion of the nerve was swollen. Clinical improvement followed three weeks later (11 weeks from the onset) but never became complete. Five months after the onset electromyography showed some motor unit potentials and no fibrillation potentials.

Case 99.—A 14-year-old girl suffered a complete right facial paralysis with mastoid pain. The strength–duration curves showed a shift to the right in four weeks and at eight weeks a slight improvement, but as there was no clinical improvement decompression was carried out. The nerve was swollen. At 12 weeks from onset there was a sudden return of the strength–duration curves to normal, preceding by two weeks clinical improvement of the face. When she was last seen seven months from the onset, recovery was incomplete but continuing.

Case 92.—A woman of 28 suffered a complete right facial palsy associated with herpes and vertigo. Though told that it was a forlorn hope, she was anxious for everything possible to be done, and decompression was undertaken at 16 weeks, when the nerve was found to be atrophic. No recovery was found in the ensuing 12 months.

By contrast, in the following two cases decompression was advised but not carried out. Nevertheless, the ultimate results would probably not have been better had the operation been performed.

Case 54.—A woman of 26 suffered a complete right facial paralysis with otalgia and was found to have lost her taste on the right side of the tongue and soft palate. At eight weeks the strength–duration curves were to the right and there was still complete paralysis; admission was therefore arranged for decompression. When she was admitted two weeks later there was slight voluntary movement in the orbicularis oculi, and the operation was cancelled. Steady improvement occurred, both clinically and in the strength–duration curves, and 12 months later her face was normal except for a slight weakness of the lower lip.

Case 88.—A man of 34 suffered a complete right facial paralysis with otalgia and vertigo. As there was no improvement and the strength–duration curves showed a shift to the right, decompression was advised at eight weeks. For domestic reasons he was not admitted at once, and was seen at 13 weeks, when there was voluntary movement in all parts of the face. A year later the strength–duration curves were normal and his facial movements nearly so.

While no valid generalization could be made about the value of decompression on the evidence of three cases operated on at eight weeks from the onset, and two cases in which the operation seemed indicated but was not performed, it seems likely that complete recovery would not have been achieved in Case 28 had the patient been treated conservatively, and that in Cases 86 and 99 a comparable result would probably have been achieved without operation. Those who advocate decompression agree that in the cases they select for operation incomplete recovery is to be expected whatever method of treatment is adopted, but maintain that operation produces more complete recovery. Many surgeons relate personal experiences of cases where recovery follows so closely after operation that they are convinced of a cause-and-effect relationship, but in view of the high rate of spontaneous recovery shown in this and other series at about the time when operation is usually advised, my view is that the question of the value of decompression must remain an open one.

Finally, the following case is of interest as it raises the possibility of a further avenue to be explored.

Case 21.—A woman of 67 suffered a complete right facial paralysis associated with vertigo; herpes on, below, and behind the pinna; and paresis of the right vocal cord. Owing to the appearance of fluid in the tympanic cavity, conductive deafness, and radiological changes in the mastoid, a cortical mastoidectomy was performed three and a half weeks from the onset. The bone was found to be vascular and soft, and the cells to contain blood-stained exudate. The facial nerve was not exposed. Within two days facial movements were apparent and she proceeded to complete recovery within seven weeks.

Tumarkin (1936) described a very similar case where he performed an extensive cortical mastoidectomy in a patient with Ramsay Hunt's syndrome and obtained immediate improvement in the paralysis and relief of pain.

Kettel has quoted a case of Flodgren's, where a cortical mastoidectomy was performed in a case which he regarded as Bell's palsy. The paresis was noted to improve immediately blood-stained fluid was aspirated from the mastoid cavity.

Conclusion

A large field of inquiry still exists to determine the most satisfactory methods of treating Bell's palsy. Owing to the high rate of spontaneous recovery, valid conclusions can be drawn only from a large-scale clinical investigation with adequate controls as suggested by James and Russell (1951) and by Kettel (1959). Such an investigation should aim at evaluation of the following: (1) Cervical sympathetic block in the earliest stage of the condition, as advocated by Korkis (1959). (2) "Vascular decompression" by extensive cortical mastoidectomy (Tumarkin, 1936, 1951) in severe cases where otoscopic or radiological evidence of fluid in the middle-ear cleft is forthcoming. (3) In cases of delayed recovery, decompression of the nerve as soon as electromyography indicates (by fibrillation potentials) that degeneration is beginning (Kettel, 1959).

Summary

There is evidence that some cases of Bell's palsy are due to zoster infection. Therefore it was felt that, in a series of cases of Bell's palsy, manifest cases of Ramsay Hunt's syndrome (herpes zoster oticus) should be included.

The prognosis for recovery of facial function is worsened by pain and associated nerve lesions at the onset, but the extent to which the branches of the facial nerve itself are clinically involved has no prognostic significance except possibly in the case of lacrimal hyposecretion.

Incomplete and short-lived paralysis carry a good prognosis for complete recovery.

Current views on the pathological processes involved are presented and the value of electrodiagnostic tests is discussed.

No clear evidence emerges from this series to prove the value of facial-nerve decompression, and there is a strong case for a large-scale clinical investigation to evaluate this and other methods of treatment.

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A NEW TREATMENT OF ANOREXIA NERVOSA

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Ever since Gull (1874) first described anorexia nervosa it has continued to present difficulties to general physicians and psychiatrists alike. A great deal has been written about the condition, many detailed psychiatric and endocrinological studies have been made, but little advance in treatment has occurred. Early on, Gull recognized that the patient's refusal to eat was due to "a morbid mental state" and "the inclinations of the patient must be in no way consulted . . . patients should be fed at regular intervals and surrounded by persons who would have moral control over them; relatives and friends being generally the worst attendants." He thought the prognosis was on the whole a favourable one, but doctors have since found these patients very unwilling to eat despite all the "moral" and other kinds of persuasion given. In recent years frank pessimism has sometimes been expressed about the eventual outcome of treatment. A recent study from the Maudsley Hospital showed that 15% of patients in the group followed up had died from the illness or its complications.

Hormone preparations, including thyroid, insulin, and cortisone, have all been tried with little effect. Electric shock has frequently been given, but the results are far from encouraging, and more harm than good may be done unless there is marked endogenous depression. Because of the unsuccessful results of treatment in so many patients, one of us (Sargant, 1951) treated selected chronic cases by modified leucotomy, and suggested that this was preferable to the much graver risks of allowing states of inanition to continue indefinitely. Since then the fashion in treatment has returned almost to where it started. In Gull's time, tube feeding was sometimes used as a last resort, but most workers since then have agreed that it is most undesirable from a psychological point of view. Yet within the last two years papers have again been published advocating a routine use of tube feeding as the most practical and best alternative to modified leucotomy (Williams, 1958; Wall, 1959).

In a letter on the general undesirability of tube feeding in this disease, we mentioned the use of a new method of treatment in which modified insulin treatment was combined with large doses of chlorpromazine (Dally, Oppenheim, and Sargant, 1958). We have found this method to be far more effective and simple than any other we have tried. For many years we used modified insulin alone in the treatment of anorexia nervosa, but with very little success. Then N. Moore, in a personal communication to one of us (W. S.), said that, while investigating the use of reserpine in schizophrenia at St. Patrick's Hospital, Dublin, he had also noted its value in the treatment of certain cases of anorexia nervosa. The use of reserpine, however, produced states of severe depression in some of our patients, and this led us to try chlorpromazine instead. Then we started to combine chlorpromazine with the modified insulin treatment. This paper now reports the first 20 cases of anorexia nervosa treated by this combined method over the past three years, and compares results with those obtained in 24 similar cases, all referred for a psychiatric opinion, and treated in St. Thomas's Hospital by other methods over the past 20 years. Table I compares these two groups of patients.

TABLE I.—*A Comparison of Patients of Groups A (Chlorpromazine and Insulin) and B (Other Methods)*

	Group A	Group B
Average age at onset of illness . .	18·8 ± 5·5 years	18·0 ± 5·2 years
,, weight lost before treatment	37·1 ± 15·1 lb.	33·5 ± 10·3 lb.
,, length of illness before treatment at S.T.H.	49 ± 71 months	22 ± 18 months

Selection of Patients

Anorexia nervosa is a syndrome which needs to be clearly defined. We regard the essential criteria for its diagnosis to be: (1) refusal to eat, whether or not accompanied by anorexia at the start; (2) severe loss of weight; (3) absence of evidence of schizophrenia, severe depression, or organic disease; and (4) amenorrhoea of at least three months' duration in female patients. Eventually most cases of anorexia nervosa will also develop

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obstinate constipation, hypotension, bradycardia, acrocyanosis, and a new growth of downy hair on the limbs and trunk, and in many patients physical overactivity becomes marked despite extreme emaciation. One or more of these secondary signs and symptoms were present in all 44 patients. Some writers regard amenorrhoea as an essential part of a syndrome which excludes male patients by definition. Like Gull, however, we believe that male patients can be affected, though uncommonly, and one very typical male patient is included in our group of 20.

Method Used

Patients are put to bed at the start of treatment and told they must stay there until they regain near normal weight (depending on the previous weight, age, height, etc.). Thus food intake can be supervised, and risks of using large doses of these drugs in debilitated patients are minimized. Chlorpromazine is given by mouth, starting with 150 mg. a day and increasing by 75 mg. a day to the limit of the patient's tolerance. As much as 1,000 mg. a day has been needed in difficult patients, one of whom weighed only 72 lb. (32.7 kg.). If signs of Parkinsonism increase, small doses of benzhexol hydrochloride can also be added. Modified insulin therapy is also begun at once, starting with 5 units and progressively increasing the dose until the patient sweats and becomes drowsy. Then interruption takes place with a large meal. Precautions are also taken throughout the day to avoid occurrence of late hypoglycaemia. None of our patients reacted with abnormal sensitivity, though this has been thought by some to be a theoretical objection to the use of insulin in anorexia nervosa. The average morning dose in the series was 60 units, varying from 40 to 80 units according to individual sensitivity.

At first a light diet is given. It includes frequent fortified milk drinks and is steadily increased from 1,500 calories to 4,000 calories a day. In this way abdominal discomfort, a common cause of complaint in the early stages of treatment, is reduced to a minimum. The patient's confidence is gained, and reassurance is constantly given, but no attempt is made to uncover psychological problems or to deal with them until the weight is nearly normal. Then the drugs are reduced and the patient is allowed up. A week later, provided she is still eating satisfactorily, she is discharged home. Attempts are made to follow up patients for at least a year, and supportive psychotherapy with the patient in a remission seems valuable in preventing relapse. A maintenance dose of chlorpromazine may also help to prevent relapse in some patients.

Results

In order to simplify the reporting of our results, readmissions have been regarded as fresh cases. Three of our 20 patients treated by combined chlorpromazine and insulin (now termed group A) had to be readmitted once, and only one twice. Four of the 24 patients treated by other methods and by other physicians at the hospital (now termed group B) were readmitted once.

TABLE II.—*Results of Treatment*

	No.	Average Wt Gain (lb./Week)	Average Stay in Hospital
Group A	25	4·4 ± 1·3	34·9 ± 12·2 days
,, B	28	1·3 ± 1·6	58·4 ± 6·4 ,,
Williams (1958) (patients intubated)	8	2·8	67·6 days
Stafford-Clark (1958) (mainly psychotherapy)	19	1·9	150 days (approx.)

It will be seen from Table II that the patients in group A gained an average of no less than 4.4 lb. (2 kg.) a week, and their average stay in hospital was only 34.9 days. This compares with the patients of group B, who gained an average of only 1.3 lb. (0.58 kg.) a week during an average stay of 58.4 days. The difference between these results is highly significant ($p > 0.01$). Individual details of our group A patients are given in Table III.

In the past, a weight gain of 2 lb. (0.9 kg.) a week or more has been regarded as a very satisfactory result (Ormerod, 1910). Williams (1958), reporting a series of cases treated at the London Hospital, concluded that only tube feeding produced satisfactory results, but eight such cases of his gained only an average of 2.8 lb. (1.27 kg.) during an average of 67.6 days. Stafford-Clark (1958) has also reported a group treated mainly

Insulin 5 units b.d.
Insulin 10 units b.d.
Insulin 15 units b.d.
Insulin 20 units b.d.
Insulin 30 units b.d.
Insulin 40 units b.d.
Insulin 40 units b.d.+chlorpromazine 50 mg. t.d.s.
Insulin 60 units o.m.+chlorpromazine 75 mg. t.d.s.
Insulin 60 units o.m.+chlorpromazine 125 mg. t.d.s.
Insulin 60 units o.m.+chlorpromazine 200 mg. t.d.s.
Insulin 60 units o.m.+chlorpromazine 200 mg. q.d.s.
Insulin 60 units o.m.+chlorpromazine 150 mg. q.d.s.
60 units o.m.+chlorpromazine 150 mg. t.d.s.
60 units o.m.+chlorpromazine 100 mg. t.d.s.
Insulin 40 units o.m.+chlorpromazine 50 mg. t.d.s.
20 units o.m.+chlorpromazine 25 mg. t.d.s.
7st.
6 st. 7 lb.
6 st.
5 st. 7 lb.
5 st.
Allowed up.
Discharged home.
Treated in a general ward.
Transferred to psychiatric unit.
Investigations.
Insulin begun.
Chlorpromazine combined with insulin.
17 19 21 23 25 27 29 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 2 4 6 8 10 12 14 16 18 20 22 24 26 28
June
July
August

FIG. 1.—Treatment and resultant change in weight in girl with anorexia nervosa.

TABLE III

Case No.	Sex	Age of Onset	Weight Loss lb.	Weight Loss kg.	Months of Illness	Previous Admissions	Weight Gain lb.	Weight Gain kg.	Days of Treatment
1	M	12	24	10·9	24	0	24	10·9	38
	(readmission)						16	7·3	25
2	F	11	N.K.		240	4	32	14·5	63
3	F	21	28	12·7	240	2	11	5·0	21
4	F	16	21	9·5	126	4	21	9·5	46
*5	F	18	24	10·9	16	0	12	5·4	33
6	F	15	34	15·4	13	0	15	6·8	29
	(readmission)						30	13·6	47
							12	5·4	16
7	F	15	30	13·6	9	0	15	6·8	31
8	F	17	26	11·8	48	0	20	9·1	35
9	F	27	N.K.		72	4	4	1·8	16
						(transferred due to closure of ward)			
10	F	18	28	12·7	24	0	15	6·8	24
11	F	16	29	13·2	3	0	28	12·7	46
12	F	14	38	17·2	9	1	20	9·1	29
13	F	17	30	13·6	6	0	24	10·9	26
*14	F	14	48	21·8	5	0	36	16·3	35
	(readmission)						11	5·0	21
*15	F	15	80	36·3	15	1	37	16·8	39
16	F	21	45	20·4	24	0	28	12·7	40
	(readmission)						14	6·4	27
*17	F	20	47	21·3	17	1	34	15·4	40
18	F	20	N.K.		36	3	29	13·2	62
19	F	33	N.K.		36	1	17	7·7	28
*20	F	28	46	20·9	18	0	47	21·3	55

* Treated in a general medical ward.

TABLE IV.—*Follow-up Results*

	Group A	Group B
Good recovery (menstruation and weight satisfactory)	11	13
Fair recovery (condition stable, but underweight and absent periods)	3	6
No recovery or frequent relapses	3	3
Dead	0	2
Discharged within the last three months and not therefore assessed	3	—
Total	20	24

by psychotherapy who gained an average of only 1.9 lb. (0.8 kg.) over nearly 150 days.

The results of the follow-up are shown in Table IV.

Discussion of Results

Most patients begin to gain weight almost at once when treated with the combination of chlorpromazine and insulin. An example is shown in Fig. 1. This girl was treated for 40 days with insulin before meals, during which time she gained only 3 lb. (1.4 kg.). She was then given chlorpromazine and modified insulin, and her weight rose rapidly. Fig. 2 shows a patient whose "belly touched her backbone" on admission; she was depressed, untruthful, and resisted all attempts to make her eat. After five weeks' treatment she became cheerful, co-operative, and almost normal again after a gain in weight of 20 lb. (9 kg.).

Some of the large initial weight increase is undoubtedly due to water retention, but we regard this as a favourable sign, and it is usually accompanied by increasing cheerfulness and more ready acceptance of treatment. The underlying worry about eating often persists, but no longer frightens the patient to the point of self-starvation. It seems to be the *combination* of insulin and chlorpromazine that is so effective, for neither drug given alone, nor given with an insufficient dosage of the other, produces as good results. What is more, if either the chlorpromazine or the insulin is stopped before the weight is satisfactory, or if the patient is allowed up and about too soon, she is likely to relapse. Putting the patient back to bed and replacing either drug in proper amounts will quickly reverse this tendency.

With the patient totally confined to bed and given very careful nursing, no complications have so far been encountered. But late hypoglycaemia can occur if the patient is left too long unobserved, and the hypotensive effects of chlorpromazine in such large doses in emaciated persons can be severe if the patient is allowed up too early. A good ward sister who is firm but kindly, and sees that all food given is really eaten, contributes to the success of the method, and the doctor may still at times need to apply "moral" pressure as in Gull's day. The treatment tends to fail if any one part of it is omitted or is given too much emphasis at the expense of another. However, in order to dispel any idea that our results were due solely to a well-staffed and specialized ward (though this can be very helpful), we must mention that 5 of our 20 patients have also been treated in the general medical wards of St. Thomas's Hospital. These five are marked in Table III, and have obviously done just as well as those treated in our own psychiatric beds.

FIG. 2.—Photographs of patient before and after treatment.

Follow-up of treated patients for at least a year or more after apparent recovery appears to be desirable. The view that all is well once the periods have returned is not always correct, and some of our patients have relapsed even after the return of regular menstruation. But in general we are much more satisfied with our results and follow-up findings since using this particular method of treatment, though we realize that much more time will be needed to assess its full and lasting effects on the natural course of the illness.

Summary

A new method of treatment of anorexia nervosa is described which combines the use of large doses of chlorpromazine with modified insulin treatment carried to the point of sweating and drowsiness. The patient is also confined totally to bed until the weight is nearly back to normal. The treatment of 20 patients by this method is reported, and results are compared with those obtained in 24 similar patients treated in St. Thomas's Hospital by other methods and with published results from other hospitals. It has been found more effective than any other form of treatment used previously.

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CLINICAL EVALUATION OF BENZTHIAZIDE, AN ORAL DIURETIC

BY

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The synthesis of chlorothiazide has stimulated the search for other substitution derivatives of the benzothiadiazine nucleus in the hope that these newer compounds might be less prone to induce potassium depletion. The newest compound belonging to this group is benzthiazide (3 - benzylthiomethyl - 6 - chloro - 7 - sulphamyl - 1,2,4 - benzothiadiazine-1,1-dioxide) (Fig. 1). The mode of action of chlorothiazide has been studied extensively (Bayliss *et al.*, 1958; Matheson and Morgan, 1958; Watson *et al.*, 1958), and a direct comparison with this drug provides the most satisfactory method of assessing the value of a new compound of this type.

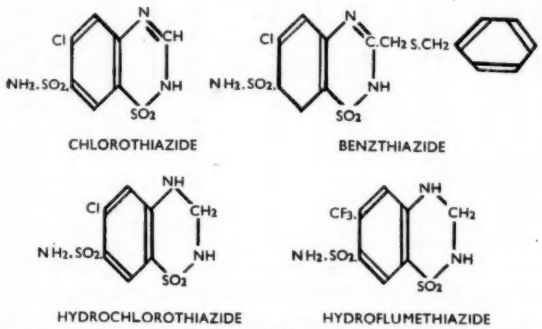

FIG. 1.—Structural formulae of principal benzothiadiazine derivatives.

Material and Methods

The action of benzthiazide as compared with that of chlorothiazide was studied in two young men admitted to hospital for the investigation of minute tuberculous foci; they had never been oedematous, and in all other respects their health was normal. The subjects continued moderate activity and no drugs other than those on trial were administered. Though dietary electrolytes were not accurately standardized, food and fluid intakes on the days of the experiments were quantitatively and qualitatively similar, and on this regime the two men had a similar pattern of electrolyte excretion. Urine was collected by evacuating the bladder at two-hourly intervals for 10 hours, and then a pooled collection was made of the urine passed in the next 14 hours. Observations were made both before and after the administration of single doses of 100 mg. of benzthiazide or 1 g. of chlorothiazide, at least three days being allowed to elapse before another experiment with a diuretic was made. The two-hourly specimens were collected with strict anaerobic precautions, but mineral oil was not used, as it has been observed that CO_2 is soluble in paraffin (Gambino, 1959). Without delay the *p*H, CO_2-content, and titratable acidity of these samples were determined; the volume and content of sodium, potassium, and chloride of all specimens were measured.

A clinical trial was conducted on 15 in-patients with oedema. The cause of the oedema was congestive cardiac failure in nine patients and hepatic cirrhosis in the remaining six. Fluid consumption was maintained at 1.5 litres daily and sodium intake was restricted to 25 mEq a day (1.5 g. NaCl diet). With the exception of one patient (Case 10) no potassium supplements were given. All the patients were weighed daily and 24-hour collections of urine were made throughout. The trial was introduced by a four-day control period of bed rest, but this was curtailed in a few patients because of the severity of their condition; if treatment other than diuretics was being given prior to the trial this was kept constant throughout. After the control period one of the diuretics under trial was administered for four days; an interval of two to four days without a diuretic was then allowed before administering the other drug for a further four days. The drug chosen to initiate therapy was alternated in successive patients. Daily dosage totalled 1 g. of chlorothiazide or 100 mg. of benzthiazide. Urine volume and electrolyte excretion were measured daily, and the serum electrolytes and blood urea were estimated twice weekly. Screening tests for blood dyscrasia and hepatic dysfunction were also carried out.

Technical Methods.—Sodium and potassium were estimated by flame photometry; chlorides by potentiometric titration, using a silver electrode; and carbon dioxide by a manometric method. Titrable acidity was determined by titration with N/50 NaOH, using bromthymol blue indicator; urine *p*H by a glass electrode *p*H meter; and urine bicarbonate from the carbonic acid–bicarbonate curve according to *p*H (Peters and Van Slyke, 1932).

Comparison of Action in Normal Subjects

Urine changes in the two men were similar, and the results have therefore been presented as a mean (Table I, Fig. 2).

TABLE I.—*Total 10-Hour Urinary Excretion After Benzthiazide and Chlorothiazide in Two Normal Men*

	Control	Benzthiazide (100 mg.)	Chlorothiazide (1 g.)
Potassium (mEq) ..	43	74	63
Sodium ,, ..	51	139	144
Chloride ,, ..	76	176	142
Bicarbonate ,, ..	7·8	7·7	36·8
Titratable acid ,, ..	8·3	9·9	4·7
Water (ml.) ..	1,170	1,840	2,080

Urine Volume.—After both drugs the urine flow was maximal in the first six hours and had returned to little above control values within 10 hours, though peak water excretion was slightly delayed after benzthiazide as compared with chlorothiazide.

Electrolyte Excretion.—This ran parallel to water excretion after both drugs. Sodium excretion was similar, but benzthiazide caused a greater loss of chloride.

Changes in Acidity.—Titratable acid and *p*H were little altered by benzthiazide; chlorothiazide led to the secretion of an alkaline urine during the first six hours,

but thereafter *p*H and titrable acidity were the same as on control days.

Bicarbonate Excretion.—This revealed the most characteristic difference, being greatly increased during the first six hours after chlorothiazide, whereas it was little altered by benzthiazide.

Clinical Trial in Heart Failure

Four patients (Cases 1, 4, 6, and 9—Table II) responded well to oral diuretics. Loss of weight is probably the best single index of progress, and these patients showed a mean weight loss of 5.5 kg. (12 lb.) during the combined periods of treatment with benzthiazide and chlorothiazide. The remaining five patients showed a fair or poor clinical response, with a mean loss of weight of 0.7 kg. (1.5 lb.) during eight days' therapy; these patients had been subjected to dietary salt restriction for months or years and had received diuretics for long periods.

The two drugs produced similar effects in the same patients and appeared to be equally efficacious. In all cases benzthiazide caused a loss of chloride in excess of the urinary sodium loss, whereas excretion of these ions tended to be equimolecular after chlorothiazide. Potassium loss was of the same order in response to both drugs. Serum electrolytes did not manifest any

TABLE II.—*Mean Effect of Benzthiazide* (100 *mg./day*) *and Chlorothiazide* (1 *g./day*) *on Urinary Water and Electrolyte Excretion in Nine Patients with Congestive Cardiac Failure*

Case No.	Sex and Age	Type of Heart Disease	Clinical Response to Oral Diuretics	Previous Diuretic Therapy	Period of Study*	Weight Change (kg.)	Urine Flow (l./24 Hrs.)	Mean Electrolyte Excretion (mEq/24 Hrs.) Na+	K+	Cl−	Blood Urea† (mg./100 ml.)
1	F 52	Rheumatic ..	Good	Yes	Control (2)	+1·0	1·2	13	46	50	44
					Chloro. (4)	−3·2	2·2	135	47	118	—
					Benz. (4)	−3·2	2·2	123	54	135	27
2	F 64	Ischaemic ..	Poor	,,	Control (2)	+1·0	0·9	6	27	11	68
					Benz. (4)	0	1·1	16	37	25	—
					Chloro. (4)	−0·7	1·4	57	53	55	44
3	M 58	Pulmonary ..	Poor	,,	Control (5)	+1·4	0·8	10	25	11	91
					Chloro. (4)	0	1·1	34	41	39	—
					Benz. (4)	+0·5	0·8	9	32	16	26
4	M 59	Hypertensive ..	Good	No	Control (3)	+1·0	1·1	7	30	15	68
					Benz. (4)	−4·3	2·3	159	64	172	—
					Chloro. (4)	−4·3	2·5	147	95	156	44
5	F 41	Rheumatic ..	Fair	Yes	Control (3)	+0·4	1·1	3	63	10	46
					Chloro. (4)	−0·4	1·6	46	89	84	—
					Benz. (4)	−0·3	1·6	46	89	97	44
6	F 75	Hypertensive ..	Good	,,	Control (4)	+1·0	1·0	10	30	9	56
					Benz. (4)	−3·2	1·7	94	52	115	—
					Chloro. (4)	−0·9	1·5	58	51	58	44
7	F 54	Kyphoscoliotic ..	Poor	,,	Control (1)	+0·4	0·4	2	10	8	47
					Chloro. (4)	−0·3	1·2	23	31	42	—
					Benz. (4)	−0·4	0·8	22	39	38	29
8	M 60	Pulmonary ..	Fair	,,	Control (1)	−0·3	1·0	20	22	15	107
					Benz. (4)	−0·7	1·4	36	59	47	—
					Chloro. (4)	−1·2	2·3	79	83	84	35
9	M 59	Hypertensive ..	Good	,,	Control (1)	−0·3	1·0	7	20	10	74
					Chloro. (4)	−1·1	1·3	80	43	46	—
					Benz. (4)	−1·9	1·6	92	58	100	49
Mean values (5 patients received chlorothiazide first and 4 benzthiazide first)					Control (22)	+0·62	0·94	9	30	15	
					Chloro. (36)	−1·34	1·66	73	59	76	
					Benz. (36)	−1·50	1·50	66	54	83	

* Figures in parentheses indicate number of observations.
† Values quoted are those before and after the complete trial (i.e., after the administration of both benzthiazide and chlorothiazide).

TABLE III.—*Mean Effect of Benzthiazide* (100 *mg./day*) *and Chlorothiazide* (1 *g./day*) *on Urinary Water and Electrolyte Excretion in Six Patients with Hepatic Cirrhosis*

Case No.	Sex and Age	Presenting Complaint	Serum A/G Ratio (g.%)	Previous Diuretic Therapy	Potassium Supplements (mEq/24 Hrs.)	Period of Study*	Weight Change (kg.)	Urine Flow (l./24 Hrs.)	Mean Electrolyte Excretion (mEq/24 Hrs.) Na+	K+	Cl−
10	M 54	Ascites ..	3·8/3·1	Yes	40	Control (2)	+0·5	1·0	0	41	6
						Benz. (4)	−0·5	1·4	12	130	80
						Chloro. (4)	0	1·6	11	126	54
11	F 39	Oedema ..	1·1/4·2	,,	None	Control (4)	+1·0	0·4	4	18	4
						Chloro. (4)	−1·8	0·4	8	17	7
						Benz. (4)	−1·8	0·8	13	31	13
12	F 64	Ascites ..	3·1/2·9	,,	,,	Control (4)	+0·4	0·9	2	49	30
						Benz. (4)	−2·2	1·6	36	104	143
						Chloro. (4)	−0·8	1·1	12	52	53
13	F 49	Oedema ..	1·4/3·2	,,	,,	Control (2)	−1·2	1·5	66	40	80
						Chloro. (4)	−1·9	2·1	104	64	139
						Benz. (4)	−1·1	1·9	61	71	91
14	F 67	Ascites ..	2·4/4·1	,,	,,	Control (3)	+1·3	1·3	2	38	30
						Benz. (4)	+1·4	1·1	3	74	80
						Chloro. (4)	+0·9	1·2	4	51	22
15	F 52	Ascites ..	2·3/2·4	No	,,	Control (1)	+0·9	0·5	4	13	5
						Chloro. (4)	−0·3	0·4	6	21	11
						Benz. (4)	−2·4	0·7	16	48	38
Mean values (3 patients received chlorothiazide first and 3 benzthiazide first)						Control (16)	+0·48	0·93	13	33	26
						Chloro. (24)	−0·65	1·13	24	55	48
						Benz. (24)	−1·10	1·25	24	76	7

* Figures in parentheses indicate number of observations.

disturbance in response to either drug. Blood-urea levels before the trial ranged from 44 to 107 mg./100 ml.; in all patients these levels were reduced after the administration of both drugs. There was no evidence of hepatic or haematological disorder after either drug, nor was any gastro-intestinal disturbance observed.

Clinical Trial in Hepatic Cirrhosis

All the patients studied were advanced cases with low serum albumin levels (Table III), and three gave a history of neuropsychiatric complications. Two of these had undergone a portal-systemic shunt operation some years earlier and presented with oedema but no ascites. One of them (Case 13) was the only one in whom sodium excretion during the control period exceeded the dietary intake of this ion; she was also the only patient who responded well. Therapy was associated with an increased urinary loss of sodium and chloride with little change in potassium excretion, and serum potassium levels were unaltered. In the other patient (Case 11) treatment was associated with no appreciable increase in the excretion of sodium or potassium; the blood urea rose steadily, and she died a week later in hepatic coma.

The remaining four patients had ascites which had become refractory to conservative measures, and had been referred to this hospital (Mr. Alan Hunt) for consideration of portacaval anastomosis. Treatment with diuretics was associated with an increased urinary loss of potassium and chloride and no appreciable excretion of sodium. This potassium diuresis was accompanied in two patients by a mean loss of weight of 3.2 kg. (7 lb.), but the other two failed to lose weight. In all these patients serum potassium levels fell to less than 3.5 mEq/l., and in two instances this was accompanied by drowsiness.

The quantitative response to the two drugs differed slightly (Table II—mean values); in the dosage used benzthiazide caused a greater increase in urinary volume and loss of weight. No toxic effects were observed with either drug.

Discussion

The patients included in this series provide a stringent test for any diuretic. A survey of Table II reveals that only one patient with congestive cardiac failure had not received previous diuretic therapy, and in all patients the daily excretion of sodium during the control period was less than the dietary intake (25 mEq). This is largely due to the fact that since the advent of oral diuretics most patients with early congestive cardiac failure tend to be treated at home.

Our findings suggest that benzthiazide by mouth is an effective diuretic. When compared in normal and oedematous subjects a dose of 100 mg. produced a diuresis similar to that of 1 g. of chlorothiazide. The differences between the two drugs are in the effective dosage and in their action on bicarbonate excretion. Chlorothiazide increases the excretion of bicarbonate, whereas benzthiazide does not.

The fact that chlorothiazide inhibits carbonic anhydrase was initially thought to explain the

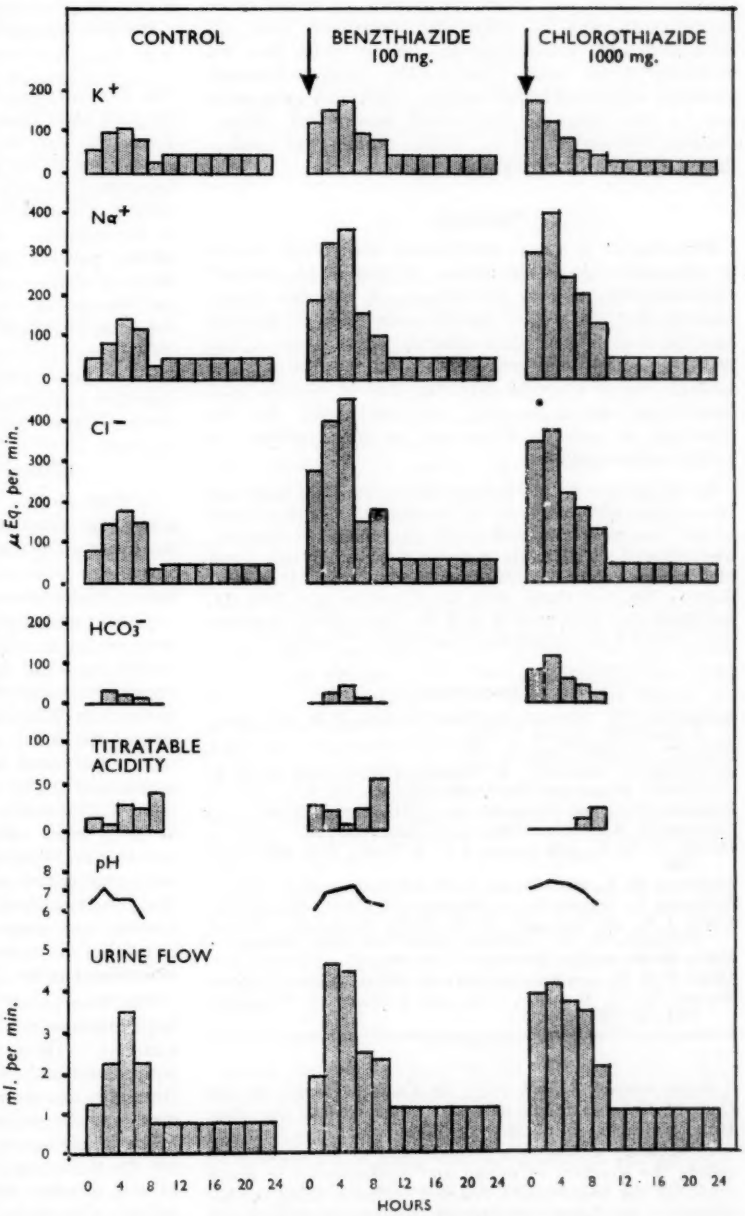

FIG. 2.—Mean effect of benzthiazide and chlorothiazide on urine volume and composition in two normal men.

hypokalaemia with which administration of this drug may be associated (Slater and Nabarro, 1958). However, hydrochlorothiazide has little inhibitory activity on carbonic anhydrase (de Stevens *et al.*, 1958) and yet its diuretic action and the tendency to cause potassium depletion are similar (Havard and Fenton, 1959 ; Platts, 1959). Hydroflumethiazide also causes less bicarbonate and more chloride excretion (Edmonds and Wilson, 1959), but the tendency to produce hypokalaemia is the same (Blagg, 1959).

We have found that benzthiazide causes a loss of chloride disproportionate to that of sodium. Bicarbonate excretion was unaltered, but potassium loss in the urine occurred just as readily. In our patients with congestive cardiac failure the mean potassium excretion after benzthiazide was 54 mEq/day, compared with 59 mEq/day after chlorothiazide. Apart from this we encountered no toxic effects. The similar chemical structure of benzthiazide suggests that this drug may not be free from the occasional hazards of chlorothiazide (Nordqvist *et al.*, 1959), though the smaller dosage may be advantageous.

Summary

Benzthiazide is a new oral diuretic chemically related to chlorothiazide. The action is similar to that of chlorothiazide, and a comparison of the two drugs suggests that 100 mg. of benzthiazide is approximately equivalent to 1 g. of chlorothiazide. The action of the two drugs differed in two ways ; after benzthiazide the urinary loss of chloride exceeded that of sodium, and bicarbonate excretion was not increased. In the treatment of oedema there was no less tendency to cause hypokalaemia.

We thank Dr. A. W. Spence for his constant help and encouragement ; Dr. J. C. B. Fenton for much helpful advice ; the consultant staff of St. Bartholomew's Hospital, who allowed us to study patients under their care ; and Mrs. Eileen Akers for many of the electrolyte determinations. We also thank Miss K. Knapman and Miss M. Robinson and their nursing staff for their willing co-operation. Pfizer Ltd. suppied the benzthiazide (" fovane ").

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In its *Annual Report, 1959*, the Central Council for the Care of Cripples refers to a controlled trial of the Spitz Holter valve in hydrocephalic children which it is financing —of necessity a long-term project—and to the problem of raising the standard of design and workmanship in goods made by the home-bound disabled. This is being further studied by the Council through its sponsorship of the newly formed Homecrafts Advisory Association.

INOCULATION OF HUMAN VOLUNTEERS WITH STRAINS OF COE VIRUS ISOLATED IN BRITAIN

BY

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The Coe virus was first described by Lennette, Fox, Schmidt, and Culver (1958), working in California. They inoculated into HeLa cell cultures extracts of throat swabs from military personnel suffering from mild acute respiratory illnesses. The virus was isolated from four patients, its presence being recognized by degeneration of the cultures. Antibody rises were detected in five further patients with similar symptoms. Apparently identical viruses were isolated in Britain in 1958 from the throats of four R.A.F. recruits with illnesses described as febrile cold, febrile sore throat, or influenza (Pereira and Pereira, 1959). Many more isolations were made under similar circumstances in 1959. This report describes experiments carried out with the Coe virus obtained from the throats of two patients in the 1959 outbreak.

Clinical and Laboratory Methods

In these studies 35 volunteers aged 18–45 years were used ; they were housed, usually in pairs, at this unit, and were observed as described by Andrewes (1948). Specimens were collected as reported by Buckland, Bynoe, Philipson, and Tyrrell (1959).

Tissue Cultures.—Human amnion cultures were prepared as described by Zitcer, Fogh, and Dunnebacke (1955) and were maintained in medium 199. Human thyroid cultures were prepared (Pulvertaft, Davies, Weiss, and Wilkinson, 1959) in test-tubes in 20% calf serum and 0.5% lactalbumin hydrolysate in Hanks's saline, and were subsequently maintained in 2% calf serum and 0.25% lactalbumin hydrolysate in Hanks's saline. HeLa-cell cultures were prepared in test-tubes in 0.1% yeast extrast, 10% human serum, and 0.5% lactalbumin hydrolysate in Hanks's saline. The cultures were maintained in 5% rabbit serum and 0.25% lactalbumin hydrolysate in Hanks's saline. The human amnion and human thyroid cultures were maintained in a roller drum at 36° C. The HeLa-cell cultures were maintained at 36° C. in stationary racks.

The Viruses.—The prototype strain of Coe virus and hyperimmune monkey serum were provided by Dr. E. H. Lennette. These were used (*a*) for neutralization tests with volunteers' sera, and (*b*) for typing viruses isolated from the throats and faeces of volunteers. The two throat swabs to be tested were immersed in Hanks's saline which was stored at −60° C. Immediately before use the fluids were diluted in Hanks's saline, and 1 ml. of this dilution was given to each volunteer as nasal drops. Coe virus was isolated from one of the throat swabs in human amnion cultures. A further passage

TABLE I.—*Effects of Inoculating Coe Virus to Human Volunteers*

Source of Virus	Dose of Virus given (TCD_{50})	No. of Volunteers Inoculated	No. of Volunteers Yielding Virus from						No. of Volunteers in Whom there was	
			Throat on			Faeces on			Antibody Rise	Illness
			Day 2*	Day 4	Day 6	Day 2	Day 4	Day 6		
Swab 67W diluted 1/10 ..	100	4	4	3	4	0	2	1	1	4
,, 94W ,, 1/10 ..	Not titrated	3	3	3	3	0	0	1	0†	3
Second tissue-culture passage of 67W	1,000	2	2	1	1	0	1		1	2
Diluted 1/100 or 1/1,000	100	2	1	0	1	1	1		0	2
Swab 94W+antiserum ..	0	2	0	0	0	0	0	0	0	0

* Volunteers inoculated on Day 0. † Paired sera obtained from only two volunteers.

of the virus was made in similar cultures to provide a pool of second-pass Coe virus grown in non-malignant human cells. Virus from this pool diluted 1/10 was completely neutralized by Coe hyperimmune serum in a neutralization test carried out in human-embryo-kidney cultures, which were observed for 12 days.

Virus Isolation.—A total of up to 0.4 ml. of fluid from a throat swab or of 10% saline extract of faeces was inoculated into human thyroid-cell cultures. A cytopathic effect was observed within seven days or else the cultures remained healthy.

Serum neutralization tests were performed in duplicate in HeLa-cell cultures, using the strain of Coe virus designated 095 from the 1958 outbreak, and in human thyroid cultures, using 100 TCD_{50} of the prototype strain of Coe virus from Dr. E. H. Lennette. The lowest dilution of serum tested was 1/10. Virus–serum mixtures were held overnight at 4° C. and at 37° C. for four hours. 0.2-ml. volumes of the mixtures were inoculated, and the cultures were observed for two weeks.

Results

The effects of the virus on the volunteers are summarized in Table I. It can be seen that illness developed in all the seven volunteers who received virus as throat-swab material and also in the four who received the virus after two passages in cultures of human amnion cells. Virus was recovered from all volunteers who became ill, except for one receiving 100 TCD_{50} of tissue-culture-passed virus. The virus was recovered most readily from throat swabs—26 out of 33 specimens were positive ; and less readily from faeces—7 of 29 specimens were positive. Seven positive throat swabs and three positive faecal suspensions were titrated in human thyroid cultures. The titres of the former ranged from $10^{1.5}$ to $10^{3.5}$ per swab (average $10^{2.4}$). The titres of the latter ranged from 10^{1} to $10^{3.5}$ per g. of faeces.

Results of serum neutralization tests were of particular interest. A rise in the content of circulating antibody was noted in only 2 of the 10 volunteers who were inoculated. Six volunteers had no detectable antibody before or after inoculation with the Coe virus. Infection occurred in spite of the presence of serum antibodies at the time of inoculation in 2 of the 11 volunteers (Table II).

The Coe virus in the fluid from swab 94W was neutralized by mixing two hours before inoculation with an equal volume of Coe antiserum at room temperature (Table I). The mixture was diluted just before inoculation to give the same final dilution of swab fluid (1/10) as in the previous experiment. The volunteers who received this inoculum were apparently not infected by the virus and did not become ill.

TABLE II.—*Variety of Antibody Responses in Volunteers From Whom Coe Virus was Recovered*

Volunteer	Antibody Titre Against Coe Virus (Strain 095)	
	Before Infection	After Infection
A*	<10	<10
B	<10	>160
C	160	640
D	320	640

* Five other volunteers shared this pattern.

The illness observed was characterized by sore throat, coryza, malaise, headache, with abdominal discomfort in some cases. In all the illnesses the clinical picture included the features of typical common colds. In four instances there was in addition an oral temperature of 99.2° F. (37.3° C.) or more—in one case reaching 100.4° F. (38° C.)—and associated general malaise and aching. The incubation period varied from two to four days (average 2.5 days). In parallel with these experiments 22 volunteers were given inocula which did not contain virus. None of them developed colds.

Discussion

Coe virus has so far been isolated from small numbers of cases of respiratory disease. As parallel control groups were not under study (Lennette *et al.*, 1958 ; Pereira and Pereira, 1959) the virus might have been harmless and accidentally present in the throat of persons suffering from "ordinary" colds. The present trials seem to show (*a*) that Coe virus infection and illness can be transmitted very readily to volunteers ; (*b*) that the ability to produce an illness can be passed along with the virus in human amnion cell cultures ; and (*c*) that neutralization of the virus by antiserum eliminates the ability to produce an illness.

We conclude that the Coe virus is pathogenic for man and causes a cold-like illness in which fever is observed more frequently than when typical colds are transmitted to volunteers. In this way it resembles the parainfluenza viruses, and, probably, the E.C.H.O. 28 (J.H. and 2060) viruses.

Summary

Seven volunteers were inoculated with Coe virus obtained direct from man, and four volunteers received virus passed twice in human amnion-cell cultures. Ten volunteers became infected as judged by recovery of virus, and 11 developed illnesses resembling the common cold. Infection occurred in spite of the presence of circulating antibody in two volunteers, and an antibody rise was detected in only two volunteers.

We thank Miss J. B. Macdonald, S.R.N., for her help in the clinical observations, and all the volunteers who took part.

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DENTAL EXTRACTIONS IN PATIENTS WITH HEART DISEASE

BY

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The management of patients with heart disease requiring dental extractions is still the subject of considerable controversy. Opinions differ regarding the nature and duration of antibiotic cover, the permissible number of extractions at any one session, the choice of anaesthesia, and the need for in-patient as opposed to out-patient treatment.

Since the classical work of Okell and Elliott (1935) on the bacteriaemia induced by dental extractions, all workers are in agreement concerning the need for antibiotic cover. Penicillin still seems to be the antibiotic of choice, but opinions vary on the extent of the cover required. Thus the American Heart Association (1955) recommends the use of one injection pre-operatively on the day the teeth are removed, whereas Hobson and Juel-Jensen (1956) prefer to continue penicillin injections several days post-operatively.

Some practitioners believe that not more than one tooth should be removed at a visit, but a search of the literature has not revealed any evidence to support or disprove this contention. Hobson and Juel-Jensen (1956) and Archer (1956) recommend the admission to hospital of all patients with heart disease for dental extractions, but others do not stress the necessity for this.

As regards anaesthesia, the choice lies between general and local anaesthesia, with or without adrenaline. Mead (1951) considers that local analgesia is best and that adrenaline is not contraindicated; on the other hand, Comroe *et al.* (1954) advise local analgesia, but prefer to dispense with adrenaline. Feldman (1946) is of the opinion that no patient with heart disease need be denied the advantages of a general anaesthetic.

This paper describes the techniques in use in the dental department at the Manchester Royal Infirmary, and is based on the management of over 300 patients with heart disease. The latter were referred direct by the general practitioner or by the department of cardiology in the hospital.

Indications for Dental Treatment in Cardiac Patients

In general the indications for extraction are those used in routine dental practice. In patients with congenital lesions or rheumatic valvular disease, however, in order to lessen the risk of inducing a subacute bacterial endocarditis, extractions have often to be done where, in the normal subject, conservative therapy is the method of choice. Thus root-canal therapy is avoided in patients with apical infections; and, similarly, in patients with parodontal disease associated with mobility of the teeth, conservative parodontal therapy, necessitating frequent gum-massage, is not undertaken. A further indication for radical treatment is the presence of dental sepsis in patients suffering from subacute bacterial endocarditis. Finally, infected teeth are removed as a precautionary measure prior to cardiac surgery, preferably two to three weeks before the operation to allow adequate healing of the sockets.

Management of Patient

Preliminary Examination. — A careful dental examination is made in every case. The time so spent is used also to establish good rapport between the operator and the patient. A calm, methodical examination, conducted in a sympathetic manner, followed by a simple explanation of the procedures to be adopted, is usually sufficient to allay the fears of all but the most nervous patient. In the latter, phenobarbitone, 90–120 mg. orally four hours before extractions, or quinalbarbitone ("seconal"), 90–180 mg. orally one and a half hours before operation, is given to dispel apprehension. The newer "tranquillizers," such as meprobamate, do not appear to afford any advantage over the barbiturates. An additional advantage of the barbiturates is their ability to depress the sensitivity of the oral mucosa.

Antibiotic Therapy.—Patients with a history of rheumatic or congenital heart disease, or who gave a history of a previous attack of subacute bacterial endocarditis, were originally given 0.5 mega unit of soluble penicillin one hour pre-operatively, and the same dose was repeated two hours after extraction. Many patients failed to wait for the second injection, and so it was decided to give a single injection pre-operatively, consisting of soluble penicillin 0.5 mega unit plus procaine 0.3 mega unit. The lateral aspect of the thigh is the most convenient site for injection in dental patients. During the preliminary examination, inquiry is made regarding hypersensitivity to penicillin. Where such a history exists, the patient receives 500 mg. of tetracycline six-hourly for 12 hours before and after extraction.

Anticoagulant Therapy.—For obvious reasons this is discontinued two days prior to the extractions and is resumed the day after operation.

Anaesthesia.—Local anaesthesia is used in most patients and has been found to be very satisfactory. Its use is also convenient in a busy dental clinic. A solution of 2% lignocaine with 1/80,000 adrenaline gives adequate anaesthesia. The total amount of the solution used in any one case varied from a minimum of 1.5 ml. to a maximum of 8 ml. Routine regional anaesthetic techniques, as determined by the teeth to be extracted, are used. The more sensitive regions of the mouth, such as the upper labial sulcus and the anterior region of the palate, have a surface application of a 5% lignocaine ointment, two or three minutes before the injection of the local anaesthetic. In addition, infiltration of the buccal and lingual mucosa over the appropriate teeth is carried out. It is essential that adequate time be allowed for anaesthesia to occur, and

at least 10 minutes should elapse prior to upper-jaw extractions and 15 minutes prior to extractions in the lower jaw. General anaesthesia is not without risk in the cardiac patient. In my opinion general anaesthesia is required in the very young, in the uncooperative adult, and in the presence of acute infection. Where general anaesthesia is used, a specialist anaesthetist is engaged and the choice of anaesthetic agent and method of administration are left entirely to him.

Hospitalization.—Generally speaking, the ambulant cardiac patient who is physically capable of attending the dental clinic is regarded as suitable for out-patient treatment, irrespective of the nature of the heart lesion. The conditions which govern admission to hospital are: (*a*) patients requiring either in-patient investigation or treatment for their cardiac lesion; (*b*) patients receiving anticoagulant therapy after myocardial infarction; and (*c*) patients in whom extractions are likely to be difficult —for example, those with impacted teeth or a previous history of difficult extractions. Multiple extractions, even a complete dental clearance, do not influence the decision regarding hospitalization.

Extractions.—Teeth are removed by standard procedures. After the extractions the mouth is cleaned with gauze pads, and the alveolar plates of the sockets are digitally compressed. Any remaining prominent processes of alveolar bone are removed with rongeur forceps. Where a tooth is fractured during its extraction, removal of the root is carried out with elevators, or by a surgical exposure. A gauze pad is placed over the sockets, and the patient is instructed to close the mouth, holding the pad in position for half an hour. If haemostasis is not achieved at the end of this time by means of pressure, sutures are employed. Mouth-washes are not advisable during the first 24 hours after operation, as their use in this period may interfere with normal haemostasis.

Clinical Material

During the past six years 313 patients were seen and treated in the department. In over 90% of these patients a careful follow-up was possible for a period of at least three months. It was felt that any complication or aggravation of the cardiac condition due to the dental treatment would be clinically obvious by the end of this period. No deliberate attempt was made, therefore, to observe the patients over a longer period, but in effect some 67% have been observed for periods varying from six months to six years.

In Table I the series is classified according to age and the nature of the heart lesion. Space does not permit a fuller description of the clinical state, but in the Table an attempt has been made to indicate the frequency of those features of most importance in assessing clinical severity of the heart lesion. Under the heading "congenital heart disease" are included patients with Fallot's tetralogy, the Eisenmenger complex, tricuspid atresia, patent ductus arteriosus, and various septal defects. The group called "chronic valvular disease" comprises patients with an acquired valvular defect, either stenosis or incompetence. The valvular lesions in this group are mainly the sequelae of rheumatic carditis, and the commonest lesion is mitral stenosis. Four patients had aortic incompetence due to syphilis. Only one patient in cardiac failure due to pregnancy complicating chronic valvular disease was encountered, and she was not thought suitable for dental treatment.

Eighteen patients were seen who gave a past history of subacute bacterial endocarditis, associated with either a congenital heart lesion or rheumatic valvular disease. Eleven patients received dental treatment during an attack of subacute bacterial endocarditis.

The last group consists of patients with essential hypertension or with atheromatous disease of the coronary arteries. Those labelled coronary artery disease gave a history of one or more attacks of myocardial infarction.

Observations and Incidence of Complications

In the group as a whole the most striking feature from the dental aspect was the extent of the caries. These patients, when compared with a similar group of healthy people, appeared to have suffered much before seeking dental treatment. Thus it was by no means uncommon to encounter exposed pulps. As a result of this delay one saw many grossly infected mouths. Contrary to what might be expected, the incidence of congenital anomalies of the teeth in patients with cardiac lesions of developmental origin was no higher than in the general population. This clinical observation was confirmed in most patients by either radiological or histological examination, or both.

In patients with cyanosis due either to congenital heart disease or to congestive failure, and in patients with hypertension, excessive post-extraction haemorrhage was occasionally encountered. Such bleeding, except in one patient, was readily controlled by simple local measures such as digital compression of the gums or suture. The exception was a patient who had suffered from a mild degree of chronic congestive failure for about 18 months. This patient bled for 48 hours after the removal of two molar teeth. Investigation of his haemostatic process revealed a marked deficiency of factor VII and prothrombin, presumably due to liver damage as a result of the long-standing congestion of that organ. The haemorrhage was eventually controlled by the parenteral administration of vitamin K_1 and the local application of thrombin. An alarming prolonged haemorrhage was encountered in a child aged 8 years with Fallot's tetralogy. In this patient, in order to avoid the administration of two general anaesthetics, the removal of eight deciduous molars had been undertaken immediately prior to tonsillectomy. Slight oozing from the tonsillar beds resulted in continuous coughing, causing haemorrhage from the sockets. With haemorrhage occurring from both sources, it was difficult to treat either adequately, and before haemostasis was finally achieved a blood transfusion had to be given.

TABLE I.—*Classification of* 313 *Patients with Heart Disease*

Age Group	Congenital Heart Disease		Chronic Valvular Disease			Ischaemic Heart Disease		
	Cyanotic	Non-cyanotic	Compensated	Complicated by Pregnancy	In Congestive Failure	Coronary Artery Disease	Hypertension	Hypertension with Angina
Children	45	14	—	—	—	—	—	—
Adults	20	13	148	15	13	20	18	7

Despite the previously noted high incidence of sepsis the number of "dry sockets" seen was not excessive. Apart from the patients who developed "dry sockets," wound-healing was not delayed.

No case of sudden death in the chair occurred. One patient with the Eisenmenger complex died 10 hours after coming round from the anaesthetic. This was a child, aged 6 years, who had had cardiac catheterization performed prior to removal of the teeth, under the same anaesthetic.

In the first 24 hours after extraction no patient developed myocardial infarction.

Three patients with coronary artery disease died as a result of coronary thrombosis at intervals varying from two to four months after the extractions. It was felt that these deaths were not attributable to the dental operation.

One patient with hypertension developed paroxysmal tachycardia 48 hours after a dental clearance for gross sepsis. No other serious disturbance of the heart rhythm, such as fibrillation, gallop rhythm, etc., attributable to the dental treatment, was encountered in any other patient in the group. No paradoxical embolism followed dental extractions in the patients with congenital septal defects.

Subacute bacterial endocarditis did not develop within three months of the dental extractions in any patient. Occasionally in the presence of gross sepsis some patients showed a slight pyrexia up to 99° F. (37.2° C.) in the 24 hours after extractions. Unfortunately, routine post-operative blood cultures were not possible in all patients. In those in whom it was carried out the cultures remained sterile. The majority of patients in whom white-cell counts were carried out showed a slight transient rise in the polymorphonuclear count.

Eleven patients with dental sepsis were being treated for subacute bacterial endocarditis.

None of those patients who were pregnant suffered abortion or miscarriage within four weeks of the extractions.

Discussion

In the patient with heart disease no operative procedure is without danger. The risks involved are now well known and are to a certain degree dependent upon the nature of the heart lesion. For obvious reasons, any suggested method of management should combine the maximum protection against these risks with the minimum trouble to the dentist and discomfort to the patient. Elaborate schemes of antibiotic cover, compulsory admission to hospital, and difficult anaesthetic procedures are apt to break down under the stress in busy dental departments. It was decided, for these reasons, to simplify the procedure so far as was possible. The relative freedom from complications in the 313 patients treated justifies the simple technique adopted.

General anaesthesia, even in expert hands, has a slight but definite mortality rate, irrespective of the nature of the operation. The administration of a general anaesthetic to a cardiac patient should be carried out by a specialist anaesthetist under hospital conditions. The usual general anaesthetic procedure possible in dental practice often leads to some degree of anoxia, and this must be avoided at all costs in the patient with heart disease. In the co-operative patient general anaesthesia is not often necessary, and in this series it was almost entirely confined to the group of children with congenital heart disease (Table II).

TABLE II.—*Relative Proportion of General to Local Anaesthesia in the Main Groups*

Anaesthetic		Congenital Heart Disease	Chronic Valvular Disease	Ischaemic Heart Disease
General	Adults ..	2	1	2
	Children	45	—	—
Local	Adults ..	31	175	—
	Children	14	—	43

It has been suggested that adrenaline should be avoided in the patient with heart disease for fear of inducing a cardiac arrhythmia or collapse. It will be appreciated that local anaesthesia induced with adrenaline-free solutions is not as intense or prolonged as with solutions containing adrenaline. Thus in some of the earlier patients in the series it was found that the use of adrenaline-free anaesthetic solutions resulted in the extractions being completed under suboptimal anaesthesia. It was felt that the alarm induced by pain, no matter how slight, was a potential danger in these patients. Only one patient developed paroxysmal tachycardia, and the use of adrenaline in the local-anaesthetic solution might possibly have been responsible. The dangers attendant on the use of adrenaline are perhaps more theoretical than actual in the concentration employed.

TABLE III.—*Treatment of Main Groups*

	Single Extraction	Multiple Extractions
Congenital heart disease	7	85
Valvular disease (with rheumatism) ..	38	138

Table III shows the number of single and multiple extractions carried out. Up to eight teeth were removed at one session. It can be appreciated from the Table and from the low incidence of undesirable sequelae in the series as a whole, that multiple extractions are as safe in the patient with heart disease as in the healthy patient. There is nothing in the results to support the view held by some practitioners that one tooth at a time should be removed. Each single extraction is an ordeal for the cardiac patient, and it is felt that such a protracted procedure is unnecessary, as multiple extractions in this series produced no more mental stress than the removal of one tooth.

In-patient Versus Out-patient Treatment.—With the criteria previously described, approximately 50% of the patients (Table IV) were considered fit for out-patient treatment. It can be seen from the Table that the number of out-patients as opposed to in-patients in each type of heart disease is about equal. The choice therefore depends on the clinical severity of the lesion rather than on its nature.

TABLE IV.—*Relative Proportion of Out-patient to In-patient Therapy in the Three Main Groups*

Type	Congenital Heart Disease	Chronic Valvular Disease	Ischaemic and Hypertensive Heart Disease	Totals
Out-patient ..	41	95	20	156
In-patient ..	51	81	25	157
Totals ..	92	176	45	313

Antibiotic Cover.—This is of the utmost importance for the patient with congenital or rheumatic heart disease. The method of administration for out-patients must be as simple as possible to avoid default by the patient. From the results recorded here a single combined injection of soluble and procaine penicillin appears adequate to prevent subacute bacterial endocarditis. Of the 11 patients with subacute bacterial endocarditis who received dental treatment, only two appeared to have become apyrexial as a result of the removal of dental sepsis. Nevertheless, it is very important that these patients should be examined dentally, and any teeth which are the seat of apical or parodontal infection should be removed. In subacute bacterial endocarditis adequate dental treatment should always be undertaken while the patient is still on full penicillin treatment. To leave infected teeth after recovery from subacute bacterial endocarditis invites a recurrence of the infection.

Summary

A simple technique for dealing with dental sepsis in the cardiac patient is described. It has been used, with few complications, in the treatment of 313 cases at the Manchester Royal Infirmary. Emphasis is laid on the simplicity of the procedure in order to encourage the cardiac patient to have dental treatment and to avoid disorganizing the routine in a busy dental clinic.

Many patients with advanced caries were treated. This was thought to be due to the patients' fear of the consequences of dental treatment on the heart lesion, or in some cases the medical adviser did not think the patient was fit to undergo dental extractions.

A simple technique is outlined. (1) Antibiotic cover is essential. One single pre-operative injection of soluble penicillin 0.5 mega unit plus procaine 0.3 mega unit is sufficient protection against the risk of subacute bacterial endocarditis. (2) 2% lignocaine with 1/80,000 adrenaline is an effective anaesthetic. The use of adrenaline is not contraindicated. General anaesthesia is necessary in some cases and should be administered by a specialist anaesthetist under hospital conditions. (3) There is no limit to the number of extractions that can be done at any one treatment. In the series of 313 patients treated, no deterioration of the cardiac condition attributable to dental treatment occurred. This justifies the adoption of such a technique as outlined in dealing with dental sepsis in the cardiac patient.

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The Empire Rheumatism Council booklet *Rheumatic Fever: A Handbook for Parents*, is available, free, to doctors only who may wish to pass it on to their patients' parents. Requests for the booklet should be made to the Council at Faraday House, 8–10, Charing Cross Road, London, W.C.2.

PERIPHERAL NEUROPATHY IN THE "COLLAGEN DISEASES"

A CASE OF SCLERODERMA NEUROPATHY

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Peripheral neuropathy is well recognized as a frequent complication of polyarteritis nodosa. Lovshin and Kernohan (1948) found "clinically significant" neuropathy in 15 of the 29 cases verified at necropsy, an incidence of 52%. The incidence among the other "collagen diseases," however, is much less.

Though Harvey *et al.* (1954) did not describe a single instance of peripheral neuropathy in their 138 cases of disseminated lupus erythematosus (D.L.E.), it is probably not as rare a complication as this would suggest. Heptinstall and Sowry (1952) and Scheinberg (1956) have each reported a case of D.L.E. verified at necropsy in which a symmetrical polyneuropathy was an early and significant feature of the disease. A clinically similar case was included in the report of Hart *et al.* (1957, Case 11). In a review of the neurological complications of 100 cases of D.L.E., Clark and Bailey (1954) stated that a polyneuropathy was a complication in three. Bailey *et al.* (1956) gave their experience in more detail. Five cases were reported, two with post-mortem examinations, in which either a symmetrical polyneuropathy (four cases) and/or a monoradiculitis multiplex (two cases) was a prominent manifestation. Scheinberg's estimate, therefore, of a 1 to 2% incidence of neuropathy in D.L.E. would not seem to be unreasonably high.

Characteristic perineural inflammatory nodules occur in a high proportion of patients with rheumatoid arthritis (Morrison *et al.*, 1947), but peripheral neuropathy has been regarded as a rare manifestation. In recent years an increasing number of papers have appeared on the development of vascular lesions typical of polyarteritis nodosa in patients with rheumatoid arthritis; and though corticosteroid therapy may be responsible for this apparent increase (Smyth *et al.*, 1959) such cases may occur quite independently of therapy (Ball, 1954). In many of these cases peripheral neuropathy has been an early and prominent manifestation of the arteritis (Ball, 1954; Sokoloff and Bunim, 1957; Kemper *et al.*, 1957). Since the vascular lesion may differ from that seen in polyarteritis nodosa (Robinson *et al.*, 1953; Rose, 1960), it remains controversial whether the arteritis is a feature of rheumatoid arthritis (Sokoloff and Bunim, 1957) or signifies polyarteritis nodosa complicating rheumatoid arthritis (Ball, 1954), so that the concept of a specific rheumatoid neuropathy remains in doubt. Hart *et al.* (1957) have considered the various aspects of this problem in their report of peripheral neuropathy in 10 cases of rheumatoid arthritis.

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The paucity in the literature of accounts of peripheral neuropathy in dermatomyositis and in scleroderma suggests that these associations are rarer than any of those already described above. Kinney and Maher (1940) found at necropsy a moderate degree of demyelination of the peripheral nerves in two cases of dermatomyositis, but neither of these patients showed signs or symptoms of a peripheral neuropathy. Walton and Adams (1958) did not have a single example of a peripheral neuropathy in their series of 40 cases of polymyositis, though at necropsy one case did disclose a small area of inflammatory cells in the perineurium of a peripheral nerve. They concluded from their review of the literature that "clinical evidence of peripheral nerve involvement is lacking in the great majority of cases of polymyositis and dermatomyositis."

In a review of the visceral manifestations of scleroderma, Beerman (1955) stated that, though a number of cases of involvement of the peripheral nervous system have been reported in the older literature, these are uncommon. Leinwand *et al.* (1954), in a study of 150 cases, and Rodnan (1959), in a personally observed series of 75 cases, have not reported peripheral neuropathy in a single instance. There is, however, the unusual case of Richter (1954) in which the signs were almost exclusively those of a severe, rapidly progressive polyneuropathy. Necropsy in this case disclosed a widespread increase in the bulk of connective tissue, particularly in the retroperitoneal tissues and peripheral nerves. Richter considered this a case of scleroderma.

In view of the extreme rarity of peripheral neuropathy in scleroderma and in dermatomyositis as compared with the other members of the "collagen diseases," we considered it important to record the following case.

Case History

A housewife aged 55 was last admitted to the National Hospital on October 20, 1958, under the care of Dr. William Gooddy. There was no relevant family history. The past history showed that from the age of 23 to 26 she had been under treatment for right apical pulmonary tuberculosis. She was then well until January, 1949, when, at the age of 46, she noticed over a few days the symptoms of aching, stiffness, and swelling of the fingers of the left hand. Ten days later she had a mild rash with cervical lymphadenopathy. A diagnosis of rubella was made. This condition subsided at the end of a week, but was followed a fortnight later by an erythematous "burning" rash which affected the skin of the entire body. Generalized exfoliation occurred after 10 days and the illness subsided within three weeks. She then noticed slight weakness of the right leg with a tendency for the right ankle to turn inwards when walking. This difficulty progressed slightly over the next two months, during which time she also had intermittent mild recurrences of the rash and lost a stone (6.4 kg.) in weight.

She was admitted to a general hospital in April, 1949. On examination there was a "seborrhoeic dermatitis" of the forehead, cheeks, and chin. The fingers of the left hand were spindle-shaped, with pain and limitation of movement on flexion, and the skin was tight and shiny. There was weakness of extension of the right knee and eversion of the right ankle. The right knee- and ankle-jerks were absent. The trachea was slightly deviated to the right and there was diminished expansion of both lungs. No other abnormal physical signs were present.

The haemoglobin, total and differential white blood counts, and routine urine examinations were all within normal limits. Serum uric acid was 3.4 and 4.2 mg./100 ml. on separate occasions. *X*-ray films of the chest showed scarring and small areas of consolidation at the right apex. *X*-ray films of the hands showed a considerable degree of decalcification of the bones of the left hand.

Physiotherapy was given and the patient was discharged from hospital after one month. The strength in the leg gradually returned, but one year after discharge she developed a sensation of pins-and-needles in the distal parts of all four limbs. Soon afterwards she noticed difficulty in identifying objects by touch, and her gait became unsteady, especially in the dark. By 1952, at the time of her second admission, she was no longer able to walk unassisted. During the interval of three years she had also experienced occasional difficulty in swallowing solid food. The rash over the upper chest and cheeks had often recurred, but there had been no further joint symptoms.

Examination in 1952 revealed a thin woman with a patchy, erythematous, scaly dermatitis over the chest. The skin over the fingers of both hands was now thin and tight. The limbs were generally wasted, but power was reduced only distally. All deep tendon reflexes were greatly reduced. Moderate impairment of pain and touch sensibility was present over the hands and below the knees. Vibration and position sense were absent in the fingers and toes and moderately reduced at the wrists and knees. The pulmonary changes were as noted previously. There were no other abnormal physical signs. The patient was discharged at the end of two months on a moderate dose of cortisone, but this treatment was without benefit and was stopped three months later.

The patient was admitted to hospital on four further occasions, the last time to the National Hospital in 1958. During the interval her disease seemed to progress less rapidly than before 1952. Constant paraesthesiae in her arms and legs were present until 1956, while the recurrent skin rash and intermittent dysphagia persisted throughout. In 1956 she noticed for the first time that when her hands were exposed to the cold the fingers became stiff and numb, with a blanched or mottled blue discoloration of the skin. On warming her hands the skin became red and she had a sensation of pins-and-needles in the fingers. During the winter of 1957 this condition was so severe that she avoided, so far as possible, the out of doors and cold rooms. At no time did she have any symptoms suggestive of cardiac, pulmonary, or renal involvement.

Last Admission

On admission in October, 1958, she was very thin and wasted. There was a generalized mild increase in skin pigmentation and well-marked palmar erythema. The skin over the fingers was tight, shiny, and atrophic, while that over the forearms, abdomen, and calves was thick and doughy, with slight pitting on pressure. The skin of the left cheek was indurated and less mobile that that on the right. There was a scaly erythematous patch of dermatitis over the upper chest. The muscle tone was diminished in all four limbs, and moderate wasting and weakness were present distally. There was gross ataxia without tremor of the limbs, especially with the eyes closed. All deep tendon reflexes were absent except for very sluggish biceps jerks. Upper abdominal reflexes were present and the plantar responses were flexor. Appreciation of pain and touch gradually diminished below the elbows and knees and was absent over the hands and feet. The sense of passive movement was moderately reduced at the hip- and shoulder-joints and absent more distally. The peripheral nerves were of normal thickness. The only abnormality of the joints was slight enlargement of the proximal interphalangeal joints of both hands. The pulmonary findings had not changed and the remainder of the general examination was negative.

The total and differential blood counts, haemoglobin, and urine examinations were normal on each of her admissions.

The E.S.R. was 30 mm./hr. in 1955, but was always below 24 mm./hr. thereafter. No L.E. cells were present on examination of the peripheral blood in 1955, 1956, and 1958. In 1958 the differential agglutination test was 1 : 8 and the latex fixation and antinuclear factor tests on the blood were negative. The serum electrophoretic pattern was normal in 1956 and 1958. Liver-function tests, E.C.G., and E.E.G. were all normal in 1958. Chest *x*-ray films were unchanged when compared with those taken in 1949. Films of the hands showed only mild generalized decalcification of the bones.

In 1955 and again in 1958 a barium swallow in the supine position revealed a slightly dilated oesophagus with greatly diminished peristaltic activity in its lower half. Barium did not pass into the stomach until the patient assumed the sitting position. There was a small hiatus hernia but no area of constriction and no gastro-oesophageal reflux. The stomach and small intestines appeared normal.

In 1955 a skin and muscle biopsy from the side of the right calf showed no abnormality of the muscle, but the epidermis was thin and showed hardly any papillary bodies. There was considerable oedema of the cutis. Nerve biopsy was refused by the patient.

Electromyography of the left deltoid and quadriceps muscles in 1958 showed normal insertion activity with a decrease in the number of motor units, which were of normal shape. These findings were thought to be in favour of chronic partial denervation without evidence of muscle disease.

The patient seemed to derive very little benefit from repeated courses of physiotherapy. A second three-months course of cortisone in 1956 was without subjective or objective improvement. At the time of her final discharge from hospital in November, 1958, she had to use a wheel-chair and was in need of a great deal of assistance from others.

Comment

The distribution of sensory loss, the distal muscle weakness and wasting, and the absent tendon reflexes all indicate that the patient had a mixed sensorimotor peripheral neuropathy. That the neuropathy was an integral part of her "collagen disorder" is apparent, since its onset coincided with the beginning of her illness and its steady progression over the next 10 years was accompanied by continued activity of the disease in the skin and elsewhere.

The classification of the "collagen disorder" in this case presents certain difficulties, particularly in deciding between dermatomyositis and scleroderma. In view of the changes in the lower oesophagus (Dornhorst *et al.*, 1954) and the absence of any evidence of a primary muscle disorder we have regarded this case as one of scleroderma. All the other features, and in particular Raynaud's phenomenon, are consistent with this diagnosis with the possible exception of the recurrent, scaly, erythematous rash.

Though D.L.E. could be responsible for the skin changes, Raynaud's phenomenon, and the early joint symptoms, there is very little else to suggest this diagnosis. At no time during the entire nine years of illness was there any evidence of cardiac, renal, or serosal involvement, nor were there any changes in the formed elements of the blood or serum proteins. Repeated tests for the L.E. phenomenon were negative. Dysphagia occurs in D.L.E. but has been accounted for either by oesophagitis and ulceration (Harvey *et al.*, 1954) or possibly mediastinitis (Baehr and Pollack, 1947).

The rash, the doughy oedema of the skin of the abdomen, the sclerodermatous changes in the hands, Raynaud's phenomenon, and the abnormalities in the skin biopsy are all compatible with a diagnosis of dermatomyositis (Domzalski and Morgan, 1955). Though dysphagia is a common complaint in dermatomyositis, the changes on barium swallow are maximal in the upper rather than the lower oesophagus, as one would deduce from the distribution of striated muscle. Everett and Curtis (1957) have described "hypopharyngeal paralysis and regurgitation of barium" in six cases of dermatomyositis, while Walton and Adams (1958) have recorded "pooling of barium in the hypopharynx" in three cases of polymyositis. Though Talbott and Moleres Ferrandis (1956) state that the oesophageal changes in dermatomyositis may be indistinguishable from those of scleroderma, Orabona and Albano (1958) consider the "presence of typical visceral changes of scleroderma (particularly oesophageal) an important datum for making an exact diagnosis." In the case described there was no support from muscle biopsy of a primary muscle disorder. So, despite the unusual rash, we feel that the evidence is more in favour of scleroderma. In either disease, however, peripheral neuropathy is of such rarity as to make this case of exceptional interest.

Discussion

Neuropathy was an early manifestation in the case presented. Limited to one extremity at first, it later regressed and then developed as a symmetrical mixed sensorimotor polyneuropathy. In the 15 cases of polyarteritis nodosa with neuropathy reported by Lovshin and Kernohan (1948), the neuropathy was present initially in seven, eight took the form of a mononeuritis multiplex, seven were symmetrical polyneuropathies, and a clear-cut regression of signs and symptoms occurred in four cases. Similar clinical features of the neuropathy have been found in cases of D.L.E. The most distinctive of these features is the involvement of single or multiple nerves in an asymmetrical fashion. Nevertheless, it is only by virtue of the association of the neuropathy with the other manifestations of the "collagen disorder" that the aetiology of the neuropathy can be determined clinically.

Since the collagenous elements of the peripheral nerves are the blood-vessels and the connective-tissue sheaths around the nerve fibres and bundles, it is not surprising that the primary pathological changes have been found in relationship to these structures. Lovshin and Kernohan found the typical lesions of polyarteritis nodosa in the arteriae nervorum of all the 15 patients who had had peripheral neuropathy clinically. Infarct necrosis of nerve bundles was commonly observed in relation to the vascular damage, with diffuse degeneration of the nerves below these lesions. The authors concluded that the neuropathy was ischaemic in origin.

Involvement of the small arteries of the nerves was also present in the case of D.L.E. described by Heptinstall and Sowry (1952) and in the first of the two cases reported by Bailey *et al.* (1956). Unfortunately, no mention of infarct necrosis of the nerves was made in either of these cases. Changes in the vessels of the nerves were not present, however, in the second case

reported by Bailey *et al.* or in the case recorded by Scheinberg, (1956), though vascular lesions were present elsewhere in the necropsy material. Scheinberg concluded that in his case a bluish staining material, perhaps related to haematoxylin bodies, which lay beneath the endoneurium and perineurium was responsible for the diffuse degenerative changes in the peripheral nerves.

The only pathological report of scleroderma neuropathy is that by Richter (1954), in which there was an increased thickness of the connective-tissue sheaths of the nerves and a heavy deposition of mucoid material between them and the nerve fibres. Though the walls of the arteriae nervorum were greatly thickened, almost to the point of occlusion, no infarct necrosis of the nerves could be found. Richter proposed that the deposition of mucoid material had led to the degenerative changes in the nerves.

The pathogenesis, then, is clearly established only for the neuropathy of polyarteritis nodosa. Further necropsy studies are needed before any generalizations can be made concerning the other "collagen diseases." Regardless of the pathogenesis of the neuropathy in these other forms, however, the incidence of neuropathy among the different types of "collagen diseases" does parallel to some extent the degree of vascular involvement found in other tissues. Though vascular lesions similar to those in polyarteritis nodosa occur in D.L.E., they are usually less severe, thrombosis is rare, and smaller arteries tend to be affected (Klemperer *et al.*, 1941). Vascular changes are least severe in scleroderma and dermatomyositis. An increase occurs in connective tissue about the vessels and there is hyalinization of the media and intima with thickening of the latter and occasional obliteration of the lumen. Fibrinoid necrosis of the vessels has also been described, but as discussed by Rodnan *et al.* (1957) this change may be a result of the systemic hypertension occurring in some patients with scleroderma who have renal involvement. Moore and Sheehan (1952) have described "mucoid intimal thickening" of the intralobular arteries of the kidney, which they think may cause acute ischaemic changes in the related cortex. In general, however, changes in blood-vessels have not been considered important in the genesis of extravascular lesions in either scleroderma or dermatomyositis.

In reviewing cases in the literature of neuropathy in "collagen diseases" it was apparent that appropriate consideration was not always given to the possibility of muscle weakness, even distal, being due to a polymyositis; of changes in the hands, particularly in rheumatoid arthritis being due to the carpal-tunnel syndrome; or of the possible role of pressure neuropathies in patients confined to bed. On the other hand, it is possible that, in scleroderma, minor sensory loss and muscle-wasting due to neuropathy may be attributed to the atrophy of the skin and soft tissues.

Summary

The case of a 55-year-old woman with ten years' history of arthritis and skin lesions followed by the development of peripheral neuropathy, dysphagia, and Raynaud's phenomenon is described. It was considered that the peripheral neuropathy was secondary to collagen vascular disease, probably scleroderma.

The differential diagnosis in this patient between scleroderma and polymyositis is discussed, and the difficulties of separating the individual "collagen diseases" are indicated.

The rarity of peripheral neuropathy in scleroderma and polymyositis is emphasized in contrast to the high frequency of this complication in polyarteritis nodosa. The literature relating to the association of peripheral neuropathy and the "collagen diseases" is reviewed and the pathogenesis of the neurological lesions discussed.

We thank Dr. William Gooddy for permission to publish this case.

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With the proportion of older workers in industry increasing it is vitally important for our economic progress that their skill and abilities are used to the utmost advantage. This is one of the main points made in *The Older Worker and his Job*, a popular and brief account of recent research in this field, and in particular of the studies reported in *Ageing and Human Skill*, by A. T. Welford. The review summarizes the advantages that come with age, such as increased experience, accuracy, loyalty, reliability. It also describes the changes, both mental and physical, which decrease individual efficiency. Suggestions for coping with the problems of ageing workers include modifying the job or a complete change of occupation. But the author emphasizes that research is far from complete and that full co-operation is necessary between those studying the subject and people in industry. (*The Older Worker and his Job*, by Hilary M. Clay. "Problems of Progress in Industry," Series No. 7. Published for the Department of Scientific and Industrial Research by H.M.S.O., price 1s. 3d., by post 1s. 5d.)

SERUM DETECTION OF CARCINOMA

EXPERIENCE WITH THE SCHULTZ–DALE TECHNIQUE

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Makari (1955, 1958), using the Schultz–Dale technique, has reported the detection of characteristic antigens in 95% of sera from patients with carcinoma, with fewer than 5% false results in non-carcinomatous patients and healthy persons. Burrows (1958) confirms this, but McEwen (1959) does not. Makari (1959) criticizes McEwen's method, and gives some previously unpublished details of his own technique.

Further independent investigation of this cancer test is very necessary. If the reliability claimed by Makari and by Burrows could be reproduced in a few more centres the test would be worth setting up, in spite of its technical difficulties, in all major medical laboratories.

We have attempted the method, and our results are reported here.

Outline of the Method.—A virgin female guinea-pig is immunized with an extract of carcinoma. After an interval the animal is sacrificed and a uterine horn is mounted in a Schultz–Dale bath of warm Tyrode solution. The contractions of the horn are recorded on a kymograph. The muscle is first desensitized with pooled normal human serum which produces an anaphylactic contraction (for the animal will have become immune to normal components in the carcinoma extract), after which a further specific contraction should occur upon challenge with serum from a carcinomatous patient. Skill is acquired slowly, and the test involves so many variable factors that it is at present most unlikely to be performed in exactly the same way in any two laboratories. Two important papers on the details of the Schultz–Dale technique are those by Dale (1913) and Coulson (1953).

Controls.—Makari (1955) stated that "a horn from an unsensitized normal guinea-pig was used as a control" and that "any serum which caused a contraction of the normal horn could not be evaluated." Burrows (1958) also used a normal horn as a control. In a later paper Makari (1958) no longer refers to an unsensitized horn, using instead the uterine horn of a guinea-pig immunized with non-cancerous human tissue. In his comments on McEwen's report Makari (1959) says that the use of a normal unsensitized control horn, upon which McEwen had relied, is a "definite misconception." He adds: "Early in our work we have used this procedure in one experiment on sera from patients with other diseases than cancer to detect a pressor effect. We have since found that, when cancer tissue antigens or sera from cancer patients are added to the unsensitized horn, positive reactions appear in many of these." If the first sentence is correct, then his earlier paper (Makari, 1955) is misleading. However, we believe that his present view is permissible, and we have adopted it. It implies that non-specific pharmacological pressor agents or responses will be revealed without using a normal-horn control, either during the preliminary desensitization of the sensitized horn with normal serum or by the fact that a contraction which follows challenge with cancer serum should be of the desensitizing type and not repeatable. In the latter case it is necessary to show that the horn is still alive at the end of the experiment, and this can be done by exciting a contraction with histamine.

Tyrode Solution.—An authoritative (*British Pharmacopoeia 1932*) standard Tyrode solution for the guinea-pig uterus is NaCl 9 g./l.; KCl 0.42 g./l.; $CaCl_2$ 0.24 g./l.; $NaHCO_3$ 0.5 g./l; $MgCl_2$ 0.0025 g./l.; dextrose 0.5 g./l. Dale (1913) reduced "the usual" 0.24 g./l. of $CaCl_2$ to half strength at 0.12 g./l. (This is the strength McEwen adopts, and is what we use ourselves.) Makari (1955) used $CaCl_2$ at 0.05 g./l., following Coulson *et al.* (1943), and refers to this (Makari, 1959) as "half strength," when in terms of Dale's original paper it could be described as quarter-strength. Makari (1959) also recommends that $MgCl_2$ should be increased to 0.1 g./l., and that the Tyrode solution should be adjusted to *p*H 7.4, and made up freshly every day.

The above points concerning controls and Tyrode solutions are mentioned in detail because many of them have been a source of confusion to us, and perhaps to others.

Materials and Methods

Guinea-pigs.—Young virgin females were used, segregated after weaning. They were taken from the stock bred in this institute in pens of about one hundred animals in a temperature-controlled animal-house. Three to six weeks after immunization they were killed by a blow on the neck and immediately exsanguinated by cutting the throat. The uterine horns were removed quickly and gently without the serous covering being allowed to dry, and placed in warm oxygenated Tyrode solution.

Tyrode Solution.—The *British Pharmacopoeia 1932* formula for the guinea-pig uterus was made up in glass-distilled water as quoted above, with the $CaCl_2$ reduced to 0.12 g./l., and adjusted to *p*H 7.4. It was not made freshly every day, the stock being held at 4° C. in a closed plastic vessel.

Schultz–Dale Bath.—A bath of 10 ml. capacity was used. (Neither Makari nor Burrows gives the bath volume, without which information the final concentration of the challenging serum in solution around the horns cannot be calculated.) The temperature of the bath was controllable to ± 0.5° C., and was usually set at 36° C. Tyrode solution at the same temperature could be run through at will for the frequent washing of the horn which is required. 95% oxygen with 5% carbon dioxide was steadily bubbled through the bath. The kymograph system had a forward-writing lever and a smoked drum. A tuberculin syringe was used to add measured doses of serum.

Antigen.—This was prepared as Makari's antigen C, sediment III (Makari, 1955), from 100 g. or more of carcinomatous or normal tissue homogenized to a 20% w./v. suspension in normal saline. The homogenate was centrifuged at an R.C.F. of 2.3 kg./*g* for 15 minutes, the sediment was discarded, and the supernatant recentrifuged at an R.C.F. of 10.3 kg./*g* for 30 minutes and the sediment retained. When centrifuged in this way the second sediment was always sufficiently fluid to be measured by being drawn into a pipette. It was then resuspended in twice its volume of Difco bacto-adjuvant complete (Freund), and the guinea-pigs were given 0.5 ml.

intramuscularly in the thigh. (Makari does not give details of the doses he injected, but in his 1958 paper he describes the resuspension of the second sediment in the original volume of saline used for the homogenate, and so his preparations may be less concentrated than those we have been using.) The antigen, not mixed with adjuvant, was sometimes stored at −20° C., but whenever possible (which was usually) it was freshly made before use.

Sera.—Serum, and not plasma, was used for all the tests on patients with carcinoma reported here. 20 ml. of blood was taken, using a glass syringe. After 12 to 24 hours at 4° C. the serum was pipetted off the clot, and stored at −20° C. for up to four weeks. Normal serum was pooled from three donors.

Results

Non-specific Contractions

During a period of eight months, while we gained general experience of the Schultz–Dale technique and Makari's application of it, we investigated non-specific contractions which sometimes occurred when normal or pathological serum was added to uterine horns, both sensitized and normal. McEwen (1959) found these contractions were a major difficulty in the method.

An experiment using 25 normal and 79 sensitized guinea-pigs, and seven normal and five carcinomatous human sera, showed that any serum could produce these contractions if added to the 10-ml. bath in a sufficiently large dose, but that the sensitivity of individual uteri in this respect varied greatly. One contracted with doses of 0.04 ml. of serum, but most of them did so only with quantities of 0.4 ml. or over. In practice, we found that with the particular Tyrode solution we had chosen very few horns would give non-specific contractions if the challenging dose of serum was regulated to 0.5 ml., and so we adopted this rule. We found that when the uteri of 35 sensitized guinea-pigs, some sensitized with carcinoma antigen and some with normal antigen, were satisfactorily desensitized with pooled human serum, not one gave a further contraction when challenged with 0.5 ml. of each of a pair from a panel of 70 normal individual human sera, each guinea-pig being tested with a different pair. We concluded from this that effects produced by individual human serum antigens not represented in the pooled desensitizing serum must be rare.

So far we have been unwilling to reduce the calcium chloride content of our Tyrode solution below 0.12 g./l., for though to do so might abolish non-specific contractility altogether in the horns as we use them, it would also lower the sensitivity of their anaphylactic responses (Coulson, 1953).

Horns from sensitized guinea-pigs gave non-specific contractions with the same average range of doses of serum as normal unsensitized horns. If the injection site became infected (as it did in a number of animals at one stage in our work when an adjuvant-antigen mixture became accidentally contaminated with *B. subtilis*) non-specific contractions became so frequent with minimal doses of serum that the preparations were useless for the Schultz–Dale method. The same happened when some guinea-pigs injured their limbs in the wire mesh of unsuitable cages.

We found no difference between serum and platelet-free heparinized plasma in the tendency to promote non-specific contractions.

Sera from Patients with Carcinoma

Sera from 49 cases of proved carcinoma were tested, using 268 guinea-pigs.

It was decided to rate a serum *positive* only if it (*a*) produced within 30 seconds a single non-repeatable anaphylactic contraction (after desensitization with normal serum) in both uterine horns (tested separately) of each of three guinea-pigs immunized with carcinoma antigen, and (*b*) failed to produce contractions in similar tests on both horns of each of two guinea-pigs sensitized with an antigen made from the tissue of a non-cancerous person. Sera were rated *inconclusive* if they gave less than the full number of specific contractions with the six horns in *a* but satisfied *b*, and *negative* if both *a* and *b* gave negative results.

23 guinea-pigs had uterine horns which gave repetitious non-specific contractions during preliminary desensitization with doses of 0.5 ml. of normal pooled human serum. These were discarded. 11 had been sensitized with carcinoma antigens, and 12 with antigens made from apparently normal organs.

Of the 49 sera from carcinomatous patients, 23 were positive (47%), 8 were inconclusive, and 18 were negative, by the criteria given above.

This experiment included an attempt to find whether there was an optimum weight or immunization period for the guinea-pig response. The range of weights of all the animals used was 270 to 510 g., with a mean of 390 g. A greater proportion (not statistically significant) of positively-reacting uterine horns was found in guinea-pigs weighing 420–450 g. No differences were noted between results in guinea-pigs sacrificed at three, four, five, or six weeks after the injection of antigen. Burrows (1958) noticed a seasonal difference in the guinea-pig response, but, so far as we could see, the effects in winter and in summer in Adelaide were the same.

Antigens were made from various carcinomata, some primary and some metastatic, of skin, breast, lung, stomach, and colon. Sera were tested from patients with carcinomata of skin, breast, palate, larynx, lung, stomach, gall-bladder, pancreas, ovary, colon, rectum, and prostate. No significant correlations with site were discernible in our results.

Discussion

Though we cannot substantiate Makari's claims concerning the accuracy of his test in cancer diagnosis, we publish the present account because it offers further confirmation (which we believe was needed) of the two main features of his work. Firstly, it has been shown that there is a difference between the responses of some guinea-pigs immunized with carcinoma antigens and the responses of others immunized with comparable antigens from non-carcinomatous organs. Secondly, these responses are excited by sera from some patients with carcinoma, and not by sera from healthy subjects.

We have not investigated a parallel collection of sera from non-carcinomatous sick people, believing that this is not worth while so long as the proportion of positive results with known carcinoma sera remains as low as 47% in our hands.

We are now using refined extracts of carcinomatous tissues, which we hope will provoke a more reliable immune response in the guinea-pigs, leading to a higher proportion of positive results in the diagnosis of carcinoma, if the substance which triggers the reaction

in the uterine preparation is indeed present in the serum of 95% of patients with cancer, as Makari claims.

Summary

A preliminary attempt to use the Schultz–Dale technique in the diagnosis of cancer has been successful in 23 cases of carcinoma, and unsuccessful in 26.

The claims of Makari and of Burrows that the test has an accuracy of over 95% have not been substantiated. On the other hand, the results can be taken to confirm the immunological basis of the method.

We are grateful to the consulting physicians and surgeons of the Royal Adelaide Hospital and of the Queen Elizabeth Hospital, Adelaide, who suggested that we should test serum from their cases; to Professor R. F. Whelan, of the University of Adelaide Department of Physiology, who gave us much assistance with the setting up of the Schultz–Dale baths and kymograph systems; and to Dr. J. Orde Poynton, Director of this Institute, for helpful interest and advice. This work was assisted by a grant from the National Health and Medical Research Council of Australia.

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THE SERUM LEUCINE AMINOPEPTIDASE TEST

AN APPRAISAL OF ITS VALUE IN DIAGNOSIS OF CARCINOMA OF PANCREAS

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Despite the multiplicity of laboratory tests of liver function the differential diagnosis of jaundice often presents a vexing problem. This is particularly true when carcinoma of the pancreas is considered, and clinicians would welcome any test which could confirm or exclude such a diagnosis prior to laparotomy.

From an annotation in the *British Medical Journal* (1958) it seemed that such a test was now available in the leucine aminopeptidase estimations as described by Rutenberg, Goldbarg, and Pineda (1958). These writers claimed that it was possible to distinguish between patients with carcinoma of the pancreas and patients with other conditions which produce jaundice, by the measurement of the leucine aminopeptidase in serum and urine.

Their results could be summarized as follows: (*a*) High serum and high urine values were obtained in all their patients with carcinoma of the pancreas (18 of head; 2 of tail). (*b*) Other causes of obstructive jaundice gave high serum values, but not nearly so high as in carcinoma of the pancreas; the urine values sometimes showed a moderate rise. (*c*) There was a moderate rise, more so in serum than in urine, in other hepatic conditions—for example, cirrhosis, hepatitis, and cholecystitis. (*d*) Where hepatic metastases were present from primary growths outside the hepato-biliary tract, moderately raised serum levels were found.

This paper is an account of the attempt to confirm the diagnostic value of this test in a large series of patients (including 15 with carcinoma of the pancreas), most of whom suffered from diseases of the liver and bile-ducts.

Method

Leucine aminopeptidase is an enzyme which splits the peptide link between leucine and other amino-acids. It is not absolutely specific, as it can also act on any N-terminal amino-acid with an aliphatic side-chain. In man, it is found in the liver, kidney, spleen, skeletal muscle, alimentary tract mucosa and contents, brain, testis, pancreas, blood, and urine. Its function in the blood and urine is not known.

Each step in the method devised by Goldbarg and Rutenburg (1958) was critically examined and verified; their method was finally adopted exactly. The principle of the method depends upon the enzymatic hydrolysis at 37° C. of a buffered substrate of L-leucyl-β-naphthylamine hydrochloride; the liberated β-naphthylamine is converted, by a modification of the Bratton and Marshall (1939) reaction, to a stable azo-dye which can then be estimated colorimetrically against a standard calibration curve prepared from β-naphthylamine hydrochloride. The test is easy to perform and needs no apparatus that will not be found in a routine clinical laboratory. The reagents are now readily available in this country. Serum can be stored at 4° C. for up to a month before analysis.

Goldbarg and Rutenburg originally defined the serum activity arbitrarily in terms of the readings on a Klett colorimeter, and the urine activity in terms of the amount of β-naphthylamine liberated under the conditions of the test. As we intended to include renal clearance studies we decided to define our serum activity more specifically and in the same manner as for urine (a unit is the number of micrograms of β-naphthylamine liberated by 1 ml. of a 2% dilution of the serum). In practice, our unit is exactly 12 times as large as that of Goldbarg and Rutenburg. These authors later redefined their unit for serum also in terms of β-naphthylamine liberated, and this new unit is also exactly one-twelfth of our unit (Goldbarg, Pineda, and Rutenburg, 1959).

A few tests were carried out at the request of our clinical colleagues, but most of the results were obtained from the examination of jaundiced serum received for other investigations and of serum in which the clinical data of the request form indicated the possibility of a condition in which the leucine aminopeptidase might be changed. Fuller clinical information was obtained later from the case-notes or from personal meetings with the clinicians in charge. We discuss only those results where a firm diagnosis could be reached on clinical grounds, together with other laboratory investigations; all cases of carcinoma of the pancreas or secondary malignant deposits in the liver had had a laparotomy or necropsy.

Altogether 870 tests have been carried out—120 on 119 normal subjects and 750 on 552 patients.

Results

Our values for the serum leucine aminopeptidase (L.A.P.) levels in normal subjects are in good agreement with those of Rutenburg *et al.* (1958) (see Table). A result over 18 units was regarded as abnormal.

Normal Serum L.A.P. Values (Units)

	Sex	No. of Subjects	Range	Mean	S.D.
A	Male ..	46	5·2–17·9	10·9	2·8
	Female ..	73	4·5–19·3	10·3	2·9
B	Male ..	200	6·3–19·1	11·9	2·4
	Female ..	60	6·7–17·5	10·8	2·3

A = Results obtained in this series. B = Results of Rutenburg *et al.* (1958), which have been converted from their "Klett" units to the units defined in this paper.

The results in conditions in which jaundice might be expected to occur are presented in Fig. 1. Each point refers to the value obtained at the first examination only, subsequent and serial estimations being excluded.

In our series of 15 patients with carcinoma of the pancreas, only one normal serum L.A.P. value was encountered. In this case no active treatment was possible, since laparotomy showed a tumour as large as a tennis ball in the head of the pancreas and many secondary deposits in the liver and elsewhere. Ten weeks later the L.A.P. level had increased from 9 to 15 units, the serum bilirubin from 0.6 to 1.3 mg./100 ml., and the serum alkaline phosphatase from 8 to 10 King–Armstrong units/100 ml. After another eight weeks, and three days before death, the levels had returned to 13 units, 0.6 mg., and 7.5 units respectively. It is worth recording at this point that in only one case of our series was a raised L.A.P. value found when the serum bilirubin was less than 1 mg./100 ml. This is unlike the experience of Rutenburg *et al.*, who indeed claim a special value for this test in the "anicteric patient." One patient had a carcinoma of the tail of the pancreas with hepatic metastases, and his serum L.A.P. level at 25 units was raised slightly above the normal range.

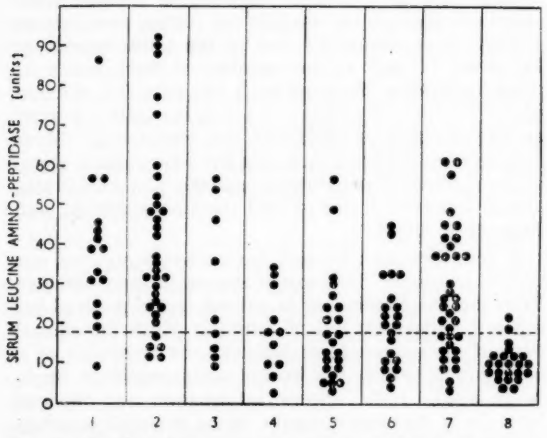

FIG. 1.—Results of serum L.A.P. values plotted as frequency distributions for the conditions investigated. Column 1 = carcinoma of pancreas; 2 = obstructive jaundice; 3 = pancreatitis; 4 = cirrhosis; 5 = infective hepatitis; 6 = acute cholecystitis; 7 = primary cancer outside the hepato-biliary tract with hepatic metastases; 8 = primary cancer outside the hepato-biliary tract without hepatic metastases. The broken line shows the upper limit of normal.

All the cases of "obstructive jaundice" (column 2 in Fig. 1) were the result of cholecystitis and its sequelae, usually cholelithiasis. They include one case of intrahepatic biliary-duct fibrosis after cholecystectomy, one of stenosis of the common bile-duct after cholangitis, and one of stenosis of the common bile-duct two years after surgery: the latter produced the highest serum leucine aminopeptidase value of our entire experience. The frequency scatter is seen to be the same as for carcinoma of the pancreas except that a higher proportion of results were within the normal range.

A similar scatter, without, however, reaching the highest levels of the first two groups, was observed in cases of pancreatitis, cirrhosis, infective hepatitis, acute cholecystitis, and primary cancer outside the hepato-biliary tract with hepatic metastases (columns 3, 4, 5, 6, and 7 respectively of Fig. 1).

Discussion

The problems of the differential diagnosis of jaundice (Reinhold, 1955) have been little affected by the introduction of the leucine aminopeptidase test. It has been especially disappointing that from our experiences we have been unable to support the statement of Rutenburg *et al.* (1958) that "assays of leucine aminopeptidase are especially definitive when normal in ruling out cancer of the head of the pancreas." It is also quite clear from the results presented in Fig. 1 that no distinction could be made by this test alone between carcinoma of the pancreas and other conditions which had given rise to jaundice. Though employing a different method of estimating the serum leucine aminopeptidase, the same conclusions had been reached by Fleisher, Butt, and Huizenga (1957): in 87 patients with obstructive jaundice they had only 62% of abnormally high values and there was no significant statistical difference among the results of three subgroups consisting of 26 cases with stone in the common bile-duct, 26 with stricture of the duct, and 35 with malignant tumours (exact sites not specified).

The main positive finding to be derived from Fig. 1 is the confirmation that there is a significant difference between patients with proved hepatic secondaries from non-pancreatic primaries (column 7) and those in whom secondaries could not be detected (column 8). Even here, however, in every instance where the serum L.A.P. was increased, so also was the established serum alkaline phosphatase test for biliary obstruction; in addition, the alkaline phosphatase could be increased in conjunction with a normal L.A.P. value.

It appeared that the serum L.A.P. test might be an indication of obstruction to the biliary flow, with no ability to distinguish between the various causes of obstruction. We decided to try to correlate our serum L.A.P. figures with those of serum bilirubin and serum alkaline phosphatase, estimated on the same sample, in patients with carcinoma of the pancreas and other obstructive jaundices.

The results showed a lack of any close correlation between the serum bilirubin and serum L.A.P. levels, thereby confirming the claim by Rutenburg *et al.* (1958) that there is no relationship between the serum L.A.P. level and the degree or duration of jaundice.

When, however, the serum alkaline phosphatase results were plotted against the serum L.A.P. values

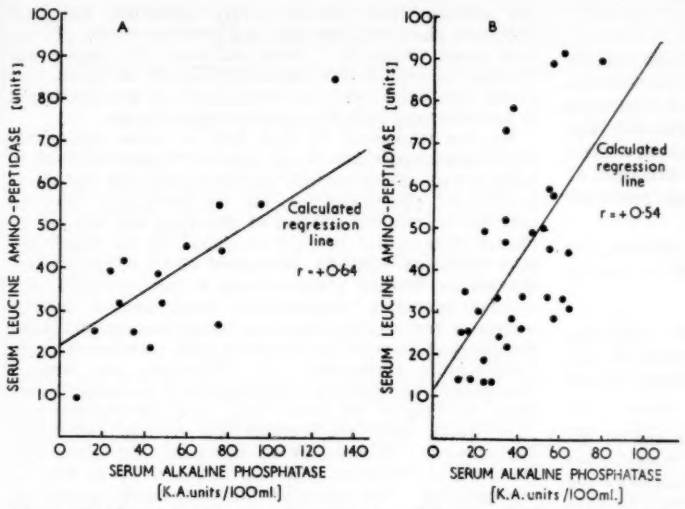

FIG. 2.—(A) Correlation between the serum L.A.P. and serum alkaline phosphatase results in cases of carcinoma of pancreas and (B) in obstructive jaundice.

a reasonably satisfactory measure of correlation was found. This correlation was better for carcinoma of the pancreas (15 patients) than for "obstructive jaundice" (33 patients) (Fig. 2). Furthermore, the calculated regression lines suggested that with carcinoma of the pancreas the serum L.A.P. lags behind the rising serum alkaline phosphatase, as compared with cases of obstructive jaundice. This finding has little value in the diagnosis of any individual case.

The difference could arise in two ways. Firstly, it could be ascribed to a lowered renal threshold for leucine aminopeptidase in cases of carcinoma of the pancreas and thereby explain the higher urinary L.A.P. excretions recorded by Rutenburg *et al.* There is no obvious reason for such a change, and indeed our preliminary urinary studies suggested that generally the urinary L.A.P. level was merely a reflection of the serum L.A.P. level. The second possible explanation is that carcinoma of the pancreas usually leads to a persistent and ever-worsening degree of obstruction, while other causes of obstructive jaundice are often remitting. It may be, therefore, that, as the unrelenting obstruction continues, the liver cells lose their ability to manufacture leucine aminopeptidase. (This theory is open to testing by the assay of enzyme in the liver cells and secretions in animals after the common bile-duct has been obstructed experimentally.) There seems to be no excess direct secretion of the leucine aminopeptidase by the pancreas itself, as a by-pass operation to relieve an obstruction, no matter its cause, leads to a progressive fall in the serum levels of the L.A.P. bilirubin, and alkaline (see Fig. 3).

Fig. 4 shows the remarkable degree of correlation which may be found in an individual patient (recurrent cholangitis) between the serum L.A.P. and serum alkaline phosphatase. However, the values may move in diverging directions; so far, it has not been possible to glean any additional information of use to the clinician from a study of these apparent discrepancies.

The alkaline phosphatase was abnormal in numerous patients with hepato-biliary disease while the serum L.A.P. persisted within normal limits. In the reverse position, in the nine instances out of our 750 tests with a raised serum L.A.P. and a normal serum alkaline phosphatase, eight already had laboratory evidence of liver dysfunction with a raised serum bilirubin.

The original workers had included studies of the urinary excretion of leucine aminopeptidase. We have made relatively few of these tests because of the difficulties involved in the collection of a proper 24-hour specimen, the inconvenience of dialysis (found later to be unnecessary if a "blank" is deducted to correct for other chromogens), and the early discovery in one of our patients who was convalescent from a cholecystectomy for gall-stones, of an excretion of 2,100 units, which is three times the highest figure recorded by Rutenburg *et al.* in carcinoma of the pancreas.

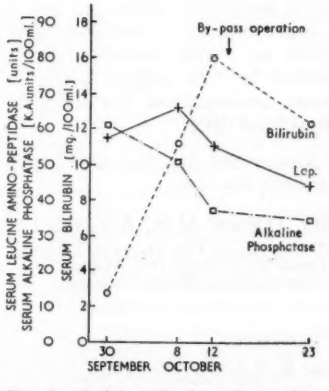

FIG. 3.—Serial studies in patients with leather-bottle stomach and secondary deposits in glands at hilum of liver, to demonstrate the divergent changes in the serum L.A.P., bilirubin, and alkaline phosphatase.

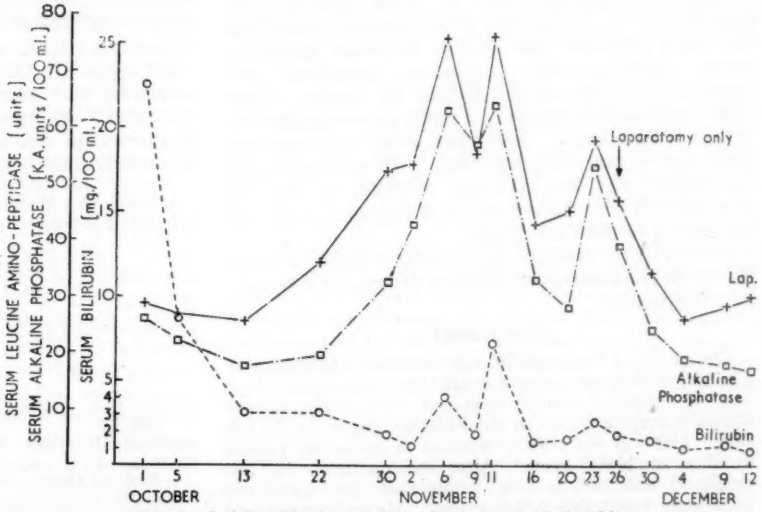

FIG. 4.—Serial studies in a patient with recurrent cholangitis.

D

Summary

Results of 750 estimations of serum leucine aminopeptidase on 671 subjects do not support claims that a normal level would exclude the diagnosis of a carcinoma of the pancreas. In our hands the test did not distinguish between carcinoma of the pancreas and other causes of jaundice; it merely denoted the presence of an obstruction to the biliary flow, without reference to the cause of obstruction.

Only extremely rarely does this test yield information not already supplied by the established tests of serum bilirubin and serum alkaline phosphatase.

ADDENDUM.—Of six further patients with carcinoma of the pancreas, tested since the compilation of this paper, five had raised values and one was within normal range.

Our thanks are due to Dr. E. M. Darmady and to the Board of the Portsmouth and Isle of Wight Area Pathological Service for enabling us to obtain a supply of the substrate before it was available in this country. We have also to thank the many clinical colleagues who co-operated in this investigation.

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Medical Memoranda

Granulocytopenia after Treatment with Phenytoin Sodium

Phenytoin sodium ("epanutin") has been used in the treatment of epilepsy for 21 years (Merritt and Putnam, 1938). During this time numerous side-effects have been described—skin rashes, cerebellar incoordination, gastro-intestinal symptoms, hirsutism, and hyperplasia of the gums. Unlike the closely related drug methoin ("mesontoin"), it rarely causes suppression of the bone-marrow. Bernhardt (1950) has described granulocytopenia after treatment with phenytoin, but his patient was also receiving methoin, so that the responsibility for bone-marrow suppression does not necessarily lie with the former.

In view of the rarity of this important side-effect after the use of phenytoin in an epileptic patient, the following case is presented.

CASE REPORT

The patient, a man aged 34, was admitted to hospital with a history of frequent epileptic attacks for about a year. There were no abnormal physical signs, but arteriography demonstrated a small angioma in the Rolandic fissure on the left side. This was successfully removed at operation, without sacrifice of brain tissue. After the operation he was dysphasic and had a right hemiparesis, but these had improved considerably within a week. He had not received any anticonvulsant therapy before admission, but after operation phenytoin, 100 mg., and phenobarbitone, 50 mg., were given six-hourly. After one week this regime was changed to eight-hourly administration of the same dose of the two drugs, and two weeks later he was discharged to convalescence with this anticonvulsant therapy.

He was readmitted 12 days later in status epilepticus. Intramuscular paraldehyde was given at frequent intervals to bring the fits under control, and phenytoin, 100 mg. three-hourly, and phenobarbitone, 100 mg. six-hourly. On the next day he received 400 mg. of phenytoin and 400 mg. of phenobarbitone, and this was continued till the fourth day after admission, when he complained of a sore throat. On examination he had a temperature of 101° F. (38.3° C.), angular stomatitis, hypertrophic gums, and a profuse growth of monilia over his palate, buccal mucosa, and gums. Haematology showed: haemoglobin, 78%; white-cell count, 2,500/c.mm.; neutrophils, 6%. Phenytoin was stopped immediately, and methoin and primidone ("mysoline") were given, the dose of the latter being increased over the next three weeks, while the methoin was reduced and finally discontinued. Phenobarbitone was continued unchanged. His monilial infection responded satisfactorily to nystatin lozenges. On the day after the cessation of phenytoin, his neutrophil count was 30/c.mm., with a platelet count of 280,000/c.mm. Twenty-four hours later his white-cell count had increased to 3,500, with neutrophils 32%, and bone-marrow examination showed normal regeneration. After a further two days his white-cell count was 7,750/c.mm., with neutrophils 75%, and subsequently remained within normal limits.

COMMENT

That phenytoin was responsible for the granulocytopenia in this patient is suggested by the rapidity with which his white-cell count returned to normal after the cessation of therapy with this drug. The condition was fortunately recognized before irreversible damage had been done to the bone-marrow.

Thirty-eight days elapsed between the beginning of treatment with phenytoin and the onset of symptoms due to granulocytopenia. The maximum daily dose that he received was 400 mg., and for more than three weeks the dose was only 300 mg. daily. The optimal dose-level is said to vary between 200 and 600 mg. daily (Goodman and Gilman, 1955). At no time, therefore, was he receiving a dosage that would be regarded as dangerous.

Methoin (5-ethyl-3-methyl-5-phenylhydantoin) has a well-marked depressant action upon the bone-marrow. Abbott and Schwab (1954) showed that in 23% of their 79 patients treated with it neutrophil counts fell below 2,500/c.mm. In view of the toxicity of this drug, it is surprising that phenytoin so rarely causes granulocytopenia. Its occurrence in this patient probably represents an uncommon constitutional sensitivity to this widely used anticonvulsant drug.

I thank Dr. Michael Kremer and Mr. Valentine Logue for their permission to publish this case.

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Reviews

CLINICAL ANAESTHESIA

A Practice of Anaesthesia. By W. D. Wylie, M.A., M.B. (Cantab.), M.R.C.P., F.F.A. R.C.S., and A. C. Churchill-Davidson, M.A., M.D.(Cantab.), F.F.A. R.C.S. (Pp. 1,056+ xv; illustrated. £5 5s.) London: Lloyd-Luke (Medical Books) Ltd. 1960.

Perhaps we have been told a little too often that anaesthesia is a rapidly advancing specialty. Yet who would have believed at the turn of the century, when massive tomes were the rule in many medical fields, that one as massive as this would one day be necessary to cover the practice of clinical anaesthesia? Dr. Wylie and Dr. Churchill-Davidson have written one of the best textbooks on anaesthesia to date, and in a manner equal to the best in any other field; it is scholarly, comprehensive, and in good literary style. The post-graduate, the specialist, and even the researcher will find the answer in full to most of their questions.

The subject matter is arranged in somewhat novel fashion, largely under the three main headings of respiratory, cardiovascular, and nervous systems—the classical tripod of Life. Within these wide boundaries the information is treated wherever possible from a physiological standpoint. To give an example. In the section on the respiratory system the authors, in separate chapters, describe the anatomy, the mechanics and physiology of respiration, lung function, the anaesthetic gases, and the examination of the respiratory tract. Only then is the reader introduced to intubation and anaesthesia for pulmonary operations. Every chapter is followed by a good selection of references, in each of which the full title of the paper is given. Seven colleagues at St. Thomas's Hospital write certain sections, notably on shock and on water and electrolyte balance by K. E. D. Shuttleworth, and on blood transfusion by M. S. R. Hutt.

The publishers have bound the book beautifully as befits one of this importance and excellence.

W. W. MUSHIN.

THE PULMONARY CIRCULATION

Pulmonary Circulation. An International Symposium, 1958. Sponsored by the Chicago Heart Association. Edited by Wright R. Adams, M.D., and Ilza Veith, Ph.D. (Pp. 316+ xv; illustrated. $4.50.) New York, London: Grune and Stratton. 1959.

This book is an excellent example of the monograph at its best. It is confined to a single subject, the pulmonary circulation, which is considered from every angle and by those who are in the forefront of the investigative attack on the many unresolved problems of the "lesser circulation." Furthermore, each contribution has been subjected to the critical appraisal of those best qualified to judge. The verbatim reports of these discussions are most stimulating and lend a quality of vivid realism.

The symposium was divided into six sections, covering the historical development of the concepts of pulmonary circulation, the physiology of the pulmonary circulation, the pathology of the pulmonary circulation, the pulmonary circulation in primary lung disease, the pulmonary circulation in congenital heart disease, and the pulmonary circulation in acquired heart disease. It is difficult to single out contributions of outstanding value from so much excellence; nevertheless it must be emphasized that great importance is placed on physical and mathematical aspects. This approach is exemplified by A. C. Burton's analysis of pulmonary haemodynamics in terms of the same factors which govern flow in peripheral vascular beds; his concept of the "critical closing pressure" is applied. A. B. DuBois contributes a delightful account of his studies on instantaneous pulmonary capillary blood-flow as measured in the body plethysmograph, with nitrous oxide as the flow indicator. Robert E. Forster provides a masterly synthesis of the volume, area, and diffusing characteristics of the pulmonary capillary bed. In this paper and in the subsequent discussion the importance of the kinetics of the $O \rightleftharpoons Hb$ reaction is emphasized. Fritts and Cournand contribute a strictly quantitative assessment of the physiological factors regulating pressure, flow, and distribution of blood in the pulmonary circulation. The same scientific approach prevails throughout all papers.

This book is essential for all workers in this field; indeed, the reviewer has purchased several copies for his laboratory. It is also to be recommended to all clinicians who aspire to understand what they are doing.

W. MELVILLE ARNOTT.

PELICAN ON EPIDEMICS

Epidemic Diseases. By A. H. Gale. (Pp. 159. 3s. 6d.) Harmondsworth, Middlesex: Penguin Books, Ltd. 1959.

This excellent book in the Pelican series is written in simple non-technical language primarily for the layman, but it can usefully find a well-deserved place on the bookshelves of any member of the profession be he student, general practitioner, or consultant.

No attempt has been made to cover each and all of the acute or common infectious diseases which have been in the past or are at the present time prevalent in the British Isles. Those diseases with a low morbidity and mortality have been excluded because of their relatively undistinguished history and blameless character. The chief criterion for the inclusion of a disease is that it has at some time been epidemic in the dictionary sense of being prevalent at one time and not at another and at its zenith associated with a high mortality.

In the introduction some doubt is suggested as to the value of this study, because five of the seventeen diseases so selected have disappeared from the present-day English scene, or have become trivial. Each of these ghost diseases, however, presents a fascinating story in its own right which illustrates the unpredictability of the changes in the virulence of a causative organism and of the immunological reactions of a host population; it also illustrates, when considered from the remedial aspect, the profound influence that improved nutritional standards and hygiene have had as contrasted with the curiously small effects of specific prophylaxis or therapy.

History repeats itself: within very recent memory there has been a most striking reduction in the mortality and morbidity previously associated with scarlet fever, diphtheria, whooping-cough, and the enteric fevers, whereas in the same period of time the toll exacted by influenza and poliomyelitis has increased in spite of the immense expenditure of research, time, and money on

prophylaxis and therapy. This book is a salutary reminder that the acute infectious diseases are not static either in their clinical manifestations or in their ability to become a scourge to human populations when some change of environment, climate, or chance variation in the causative organism fans the flame of infection into epidemic proportions.

From the beginning to the end of our professional lives we must always consider ourselves to be students, and, as such, cannot fail to find in this small book a record of events which are not only of very great historical interest as regards the past but also provocative of thought about the unpredictability of the future.

F. G. HOBSON.

RADIOGRAPHIC TECHNIQUES

Medical X-Ray Technique. Principles and Application. By J. G. Van der Plaats. (Pp. 480+xii; illustrated. 57s. 6d.) Eindhoven: Philips' Technical Library. London: Cleaver Hume Press, Ltd. 1959.

This book by Professor van der Plaats, one of the most eminent Dutch radiologists, covers the physical and biological principles in the application of *x* rays in radiodiagnosis and radiotherapy. It should prove very helpful to students, with one important caveat. The section of the book which is not good is that relating to radiation hazards. There is, first, no mention of the association of leukaemia with relatively small doses of *x* rays administered to the unborn child in such procedures as pelvimetry, and no mention of the question of threshold dose. Secondly, there is inadequate consideration of the principles of protection for the patient.

In the chapter dealing with the protection of insulated tubes one is given the impression that leaks do not occur from modern tubes, but in many departments there are modern tubes in use which are still not perfectly safe, and these may be used for many years unless juniors know how they may be tested. Likewise there is also the important matter of checking leakage from the cone or lightbeam diaphragm assembly. Even new equipment frequently shows a leak when tested under working conditions. There is no consideration of the importance of limiting off-focus or stem radiation by reduction in the size of the window of the tube—a factor which has so much to do with the limiting of scatter and gonad dose. The reader is also given the impression that he is safe provided he wears a lead apron with "adequate" lead equivalent, but it should be pointed out that this is not so unless from time to time the apron is tested when it is worn. For example, it may be found that a lead apron which is adequate for most purposes is inadequate for protection of the operator's gonads when he is standing close to a fluoroscopic *x*-ray table taking films with a high kilovoltage technique.

There is also no mention of the importance of colour vision in the preparation of the eyes for fluoroscopy: mention should be made of the type of lamps used for lighting a screening-room and the control panel. I expected to find a section on the use of *x*-ray goggles; specifying the size of the eye-piece and the colour of the material. There is also the question of glasses for those who have refractive errors or whose sight is failing. Finally, a book of this kind should include dosage tables which give some indications of the results that can be obtained in radiography, both to the skin and to the gonad area, by varying the size of field, the kilovoltage, and the filters used.

These criticisms may seem hard. They should not detract anyone from purchasing this book, but it is hoped that they may receive attention in the next edition.

F. H. KEMP.

GLAUCOMA

Symposium on Glaucoma. Transactions of New Orleans Academy of Ophthalmology, 1957. Editor: William B. Clark, M.D., F.A.C.S.; Associate Editor: Joe M. Carmichael, M.S.J. (Pp. 314; illustrated. £5 1s. 6d.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1959.

This symposium is of the didactic type. It is in no sense a round-table discussion of the controversial growing points of the subject in an attempt to reach the answers for which several people may be groping, approaching it from different routes. Rather is it a platform for teaching and therefore eminently suited for the audience that assembles at the New Orleans Academy of Ophthalmology and equally useful for the average ophthalmologist to read. The experts are there; each has delivered one or more lectures on glaucoma itself and the vast area of knowledge, anatomical, biochemical, and physiological, that borders on it: Theobald on anatomy and pathology, Swan on surgical anatomy, Becker on biochemistry, Morton Grant on aqueous production and tonography, Zimmermann on mucopolysaccharide deposits, Scheie on tonography, Haas on perimetry and provocative tests, Maumanee, Swan, and Becker on medical control; and several of these on surgical treatment. The lectures are simple and clear, and, though they contain little new, they give a well-balanced picture of the disease, its causation, pathology, and treatment as envisaged by a number of America's leading ophthalmologists.

At the end question-time arrives; queries are passed up from the audience to the experts, whose answers are given. This is the best part of the book; and certainly if they all answered them as clearly and beautifully as we read, the experts are very good indeed. Here, as often occurs, much information on incidental matter of great interest and practical importance emerges which is usually missed in formal papers or standardized textbooks. It certainly repays reading.

STEWART DUKE-ELDER.

A SIXTEENTH-CENTURY ANATOMY

A Short Introduction to Anatomy. (Isagogae Breves.) By Jacopo Berengario da Carpi. Translated with an introduction and historical notes by L. R. Lind, and with anatomical notes by Paul G. Roofe. (Pp. 228+xi; illustrated. 37s. 6d.) Chicago: University of Chicago Press. London: Cambridge University Press. 1959.

A sound knowledge of human anatomy cannot be gained without dissection of the human cadaver. For lack of such dissection anatomical knowledge languished from 300 B.C. until A.D. 1300, when Mundinus of Bologna performed dissections and wrote (in 1316) his famous *Anothomia*, thereby qualifying to be called the "restorer of anatomy." The *Anothomia* was not printed till 1493. In 1521 Berengario da Carpi published a *Commentary on the Anatomy of Mundinus*, and in the next year followed this up by publishing a dissecting

manual called *Isagogae Breves* or "a short introduction" to anatomy. As Singer has pointed out, this was the first illustrated printed textbook of anatomy. It was written in Latin, and is here translated by a classical scholar, L. R. Lind, who has also written an introduction and added some notes. Anatomical notes are given by Paul G. Roofe.

This volume is important as being a forerunner of the great work of Vesalius. The translation reads easily, but some of the terms are not easy to translate and the reader will probably have some difficulty in fully understanding the meaning of the terms "proper" and "more proper." However, there is no doubt that anatomists and medical historians will welcome this book.

Da Carpi was a well-known surgeon and anatomist, but readers of the memoirs of Benvenuto Cellini will remember the rather disparaging stories he told about Berengario. But Benvenuto's statements often have to be taken with a big grain of salt.

ZACHARY COPE.

CHILDREN WITH CEREBRAL DEFECTS

Psychological Appraisal of Children with Cerebral Defects. By Edith Meyer Taylor. (Pp. 499+xvii. 68s.) Cambridge, Mass.: Harvard University Press, Commonwealth Fund. London: Oxford University Press. 1959.

As the blurb points out, "This book is designed to help in the understanding and management of many of the serious problems that arise in children with neurological handicaps. Practical rather than theoretical, the book describes how the psychologist proceeds to evaluate the potentialities and prospects of such children, and how he interprets and uses what he finds." This is a fair assessment of both the strength and weakness of the book. Scientific measurement without theory is mere technology and often rather poor technology; the rationale of the techniques used here and often their validity are unknown or at best doubtful. Case histories ("certain typical child-patients are described through play-by-play accounts of testing situations at various age levels") may make interesting reading, but they cannot provide the necessary criterion of validity which the scientifically trained reader will look for in vain throughout the work. The author does not bother much with theories; she also does not bother much with proofs, but states opinions based essentially on experience. No doubt her experiences have been extensive and her opinions earn some respect; however, it is characteristic of science that it does not rely on such opinions but demands rigorous experimental proof. The evaluation of Dr. Taylor's work, and the use made of it, will depend entirely on the degree to which the reader is satisfied to accept her judgment and to forgo independent proof.

The newcomer to the field will certainly find a very enlightening and detailed description of the kind of test and life behaviour to be expected in children with cerebral defects, and he will have his eyes opened to many subtle interrelationships. In so far as that has been the objective of the author, she has carried out her task very satisfactorily; to demand more might be asking for something she was not prepared to give; the very demand for scientific proof might not be acceptable to an author so thoroughly clinical in her approach.

H. J. EYSENCK.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

The Plasma Proteins. Volume I: *Isolation, Characterization, and Function.* Edited by Frank W. Putnam. (Pp. 420+xv; illustrated. $12.50.) New York and London: Academic Press. 1960.

Glaucoma. Transactions of the Fourth Conference, March 8-10, 1959, Princeton, N.J. Edited by Frank W. Newell, M.D. (Pp. 257; illustrated. $8.) New York: Josiah Macy, Jr. Foundation. 1960.

Your Heart: A Handbook for Laymen. By H. M. Marvin, M.D. (Pp. 335. $4.50.) New York: Doubleday and Co., Inc. 1960.

Applications de la Médecine Psychosomatique. By P. Aboulker, L. Chertok, and M. Sapir. (Pp. 138. NF. 10.50.) Paris: Expansion Scientifique Francaise. 1960.

Symposium on the Use of Modern Diuretics in the Control of Hypertension. Held at the University of Liverpool, November 25, 1959. Edited by W. W. Heseltine and P. J. Campbell. (Pp. 85+ix; illustrated.) Liverpool: Charles Birchall and Sons, Ltd. 1959.

Bamboo Doctor. By Stanley S. Pavillard. (Pp. 206+ix; illustrated. 18s.) London: Macmillan and Co., Ltd. New York: St. Martin's Press. 1960.

Transactions of the Hunterian Society, 1958-59. (Pp. 187; illustrated.) London: Metropolis Press for the Society. 1960.

Principles of Bone X-ray Diagnosis. By George Simon, M.D., M.R.C.P., F.F.R. (Pp. 170+8+xxi; illustrated. 57s. 6d.) London: Butterworth and Co. (Publishers) Ltd. 1960.

Britannica Book of the Year 1960. (Pp. 586; illustrated. From £5 5s.) Chicago, London, Toronto: Encyclopaedia Britannica, Ltd. 1960.

Employment and Conditions of Work of Nurses. International Labour Office. (Pp. 176+vii. 12s.) Geneva: International Labour Officer. 1960.

La Biométrie. By Eugène Schreider. *"Que Sais-je?": Le Point des Connaissances Actuelles.* No. 871. (Pp. 126.) Paris: Presses Universitaires de France. 1960.

Probleme der Blutgruppenforschung. By Professor Dr. Ludwik Hirszfeld. (Pp. 160+xi; illustrated. DM. 22.) Jena: VEB Gustav Fischer Verlag. 1960.

Klinisches Lehrbuch der Physikalischen Therapie. Edited by Professor Dr. J. Grober, with nine contributors. (Pp. 442+xii; illustrated. DM. 37.75.) Jena: VEB Gustav Fischer Verlag. 1960.

Parasitologie für Ärzte. By Dr. Otto Jírovec, assisted by Dr. J. Jíra, Dr. E. Kmety, Dr. J. Kramář, Dr. M. Petrů, and Dr. B. Rosický. (Pp. 684+xi; illustrated. DM. 93.65.) Jena: VEB Gustav Fischer Verlag. 1960.

Abhandlungen über die Pathophysiologie der Regulationen. Edited by H. Kleinsorge, H. W. Knipping, and R. Wagner. Part 3: *Krankheiten der Tiefen Venen der Unteren Gliedmassen.* By Ivo Přerovský, Jiří Linhart, and Rudolf Dejdar. (Pp. 127+vii; illustrated. DM. 15.80.) Jena: VEB Gustav Fischer Verlag. 1960.

Christopher's Textbook of Surgery. Edited by Loyal Davis, M.D. Seventh edition. (Pp. 1,551+xix; illustrated. £5 19s.) Philadelphia and London: W. B. Saunders Company. 1960.

An Atlas of Neurosurgical Techniques. By James L. Poppen, M.D. (Pp. 522+xii. £9 16s.) Philadelphia and London: W. B. Saunders Company. 1960.

Histological and Histochemical Technics. By Harold A. Davenport, M.D. (Pp. 401+xxii; illustrated. 49s.) Philadelphia and London: W. B. Saunders Company. 1960.

Premature Babies: Their Nursing Care and Management. By A. K. Geddes, M.D. (Pp. 215+vii; illustrated. 31s. 6d.) Philadelphia and London: W. B. Saunders Company. 1960.

Permeability in Acute Experimental Inflammatory Oedema in the Light of the Action of Salicylates. By E. Kelemen, M.D. (Pp. 256; illustrated.) Budapest: Publishing House of Hungarian Academy of Sciences. 1960.

You and Your Eyes. By Lawrence Lewison. (Pp. 253; illustrated. $3.50.) New York: Trinity Publishing Corporation. 1960.

BRITISH MEDICAL JOURNAL
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NEW RASHES FOR OLD

There are many puzzling eruptive fevers besides the classical exanthemata of the textbooks. Those of trivial severity may rarely be seen except by the general practitioner. He may find it difficult to decide the specific diagnosis and to differentiate the condition from allergic reactions or more nebulous conditions such as "teething" or "sweat rash," not to mention minimal attacks or apparent recurrences of rubella or measles. Of these minor syndromes, those best characterized clinically are roseola infantum and erythema infectiosum.[1] Roseola infantum (exanthem subitum) typically causes sudden fever, perhaps with mild catarrhal symptoms, in infants or young children. After about three days the temperature falls to normal and a rosy rubelliform eruption appears on the neck, shoulders, and back, spreading to the abdomen and lastly to the limbs and face. Some enlargement of suboccipital and posterior cervical glands is common. The eruption generally lasts for only one or two days and is not followed by pigmentation or desquamation. The causal agent has not been identified.

Erythema infectiosum also mainly affects children. Slight feverishness and catarrh for a few days may precede the appearance of an erythematous rash affecting first the face, with a butterfly distribution over the cheeks. Next day the trunk and extremities are involved by a macular or maculopapular eruption. The facial rash fades after a few days, but that on the body and limbs may persist for more than a week, often waxing and waning, with central fading of the lesions causing a reticulated appearance. Such cases have recently been reported from the south of England by Drs. B. J. Peck[2] and A. Letchner[3] in letters to this journal. Further descriptions have been quoted in the letter from Dr. G. X. Trimble.[4]

F. Müller and A. Colli[5] report the isolation of an E.C.H.O. virus by inoculation of monkey-kidney tissue-cultures with stool and sputum specimens from cases of erythema infectiosum seen during an epidemic which affected Germany in the late summer of 1958. The virus appeared to be serologically related to the type 9 E.C.H.O. virus which has caused epidemics of aseptic meningitis and febrile illness with or without rubelliform rash in many parts of the world since the summer of 1956.[6 7 8] The eruption was reported in from under 10%[9] to around 40%[10 11] of cases of aseptic meningitis due to E.C.H.O.-9 virus. A. B. Sabin and his colleagues,[7] in an intensive study of the epidemic caused by E.C.H.O.-9 virus in Milwaukee in 1957, estimated that skin rashes appeared in the majority of infected children under 3 years old, with diminishing frequency in older age-groups, and in only 6% of cases over 15 years of age. The rash of E.C.H.O.-9 virus infection generally affects the face first and predominantly, perhaps alone, particularly the cheeks. Its resemblance to "fifth disease" (erythema infectiosum) was noted by J. F. Galpine and his colleagues.[12] The differential diagnosis of E.C.H.O.-9 virus exanthem unassociated with aseptic meningitis was discussed in a recent paper from Minneapolis describing 13 cases of rubelliform summer-rash disease infected with this virus.[8] Fever, malaise, or gastro-intestinal symptoms preceded or coincided with the onset of a rash which primarily affected the face, arms, and torso, and lasted 2 to 3 days. Pharyngitis, conjunctivitis, and cervical lymphadenopathy were occasionally noted. The white-blood and differential cell counts were usually within normal limits. These features differed from those of rubella with its paucity of prodromal symptoms, marked enlargement of post-auricular and sub-occipital nodes, and predominance of rash on the torso. They were very similar to "Boston exanthem,"[13] from which F. A. Neva isolated E.C.H.O. type-16 virus. In studies of a second outbreak of Boston exanthem, Neva contrasted the mild illness in children with the more severe disease in adults.[14] In the latter the onset of illness was generally abrupt, prostrating, and "influenzal" in character, lasting 2 to 3 days, occasionally with sore throat and abdominal pain. After subsidence of the fever a scanty macular rash appeared for 24–36 hours on the abdomen, legs, face, and upper arms. Enlargement of lymph glands was

[1] Banks, H. S., *Modern Practice in Infectious Diseases*, vol. 2, 1951, London, p. 553.
[2] Peck, B. J., *Brit. med. J.*, 1960, **1**, 877.
[3] Letchner, A., ibid., 1960, **1**, 1273.
[4] Trimble, G. X., ibid., 1960, **1**, 1568.
[5] Müller, F., and Colli, A., *Germ. med. Monthly*, 1960, **5**, 50.
[6] Boissard, G. P. B., Stokes, L. J., Macrae, A. D., and MacCallum, F. O., *Lancet*, 1957, **1**, 500.
[7] Sabin, A. B., Krumbiegel, E. R., and Wigand, R., *A.M.A. J. Dis. Child.*, 1958, **96**, 197.
[8] St. Geme, J. W., Prince, J. T., Scherer, W. F., and Krivit, W., *J. Pediat.*, 1959, **54**, 459.
[9] Jamieson, W. M., Kerr, M., and Sommerville, R. G., *Lancet*, 1958, **1**, 581.
[10] Laforest, R. A., *et al.*, *Canad. med. Ass. J.*, 1957, **77**, 1.
[11] Berglund, A., Bottiger, M., Johnsson, T., and Westermark, S., *Arch. ges. Virusforsch.*, 1958, **8**, 294.
[12] Galpine, J. F., Morrison Clayton, T., Ardley, J., and Baster, N., *Brit. med. J.*, 1958, **1**, 319.
[13] Neva, F. A., Feemster, R. F., and Gorbach, I. J., *J. Amer. med. Ass.*, 1954, **155**, 544.
[14] —— *New Engl. J. Med.*, 1956, **254**, 838.
[15] Rhodes, A. J., *Brit. med. J.*, 1960, **1**, 1071.
[16] Sanford, J. P., and Sulkin, S. E., *New Engl. J. Med.*, 1959, **261**, 1113.

not observed in adults, but occipital and posterior cervical nodes were commonly palpable in children.

Unfortunately this does not exhaust the number of E.C.H.O. viruses (and their Coxsackie and poliovirus cousins in the enterovirus group) which can cause febrile exanthems.[7–15] Each enterovirus can cause a number of different syndromes, and each major syndrome can be caused by a number of antigenically different enteroviruses. It would be surprising if clinical features would permit precise differentiation of all the enteroviruses causing febrile exanthems, particularly in sporadic cases. In a recent review J. P. Sanford and S. E. Sulkin[16] found an overlap in the clinical features of enteroviruses and were unable to distinguish eruptive E.C.H.O.-virus infections from rubella on a clinical basis. They suggested that "the predominance of any single clinical feature such as exanthems may not reflect a greater propensity for one type to produce a skin rash, but may reflect the virulence of the strain involved in an epidemic or sporadic infection as well as the susceptibility of the host." Disentanglement of this complex situation will require combined investigative attack by general practitioners, epidemiologists, and virologists.

RADIATION AND THE LEUKAEMIAS

"Leukaemia" is a collective noun like "cancer" and includes many distinguishable types of disease. Apart from running an acute or chronic course, it varies in accordance with the cell series affected—granulocytic, lymphoid, monocytic, or erythroid. There are also cross-links with other pathological conditions of the reticulo-endothelial system—for instance, the lympho-reticuloses in general and disorders of the bone-marrow such as polycythaemia vera. Thus it is probably as unhelpful to look for the "cause of leukaemia" as for the "cause of cancer." These groups of diseases seem to be the end-products of complex chains of events determined by a variety of causes, which must be laboriously separated in the attempt to understand the aetiology of the disease.

"Leukaemia" is not confined to man. Most mammals and many birds suffer from comparable conditions, so the problem of the leukaemia complex can readily be studied experimentally as well as by clinical observation. Such experimental studies indicate that among the factors which have to be weighed are exogenous chemical agents (for example, derivatives of aromatic hydrocarbons), endogenous chemical agents (particularly from the ductless glands—adrenal, reproductive, and thymus), infective agents (viruses), perhaps genetic constitution, and certainly physico-chemical damage to viable cells, especially by ionizing radiation.

Study of the roles of infective agents and radiation is very active at present. Of viruses, suffice it to say that, though relevant to the leukaemias of mouse and fowl, they have not yet been identified in these diseases in man. But there is abundant clinical evidence that exposure to x and γ rays can increase the incidence of human leukaemia, especially the acute leukaemias and chronic granulocytic leukaemia: among survivors of atomic bombs in Japan, patients submitted to radiotherapy, and some radiologists in the U.S.A. insufficiently protected in their work. More arguable is how to interpret the data obtained from surveys of subjects exposed to much smaller dosage of diagnostic x rays, either *in utero* or in later life. In all such instances the radiation is given and absorbed at a high dose-rate, which R. H. Mole[1] has shown to be more leukaemogenic in mice than the same total doses given in the same time overall.

The question arises, Is radiation given at low dose-rate a factor in the causation of human "leukaemia"? Can any human leukaemia be attributable to natural background radiation or to the yet far lower dosage from strontium-90?[2] Dr. W. M. Court Brown and his colleagues have taken advantage of the variations in background in Scotland and made surveys in an attempt to evaluate the part played by irradiation at low dose-rate. Their formidable study, published in the opening pages of the *Journal* this week, has produced interesting results. The recorded incidence of the three main types of leukaemia (but especially acute leukaemia and chronic myeloid leukaemia) is higher in Aberdeen, where the radiation background is relatively high, than the average for Scotland as a whole. The incidence of chronic lymphoid leukaemia is high in Edinburgh, where the background radiation is at an average level. In Glasgow, with a presumably average but not measured background radiation, all types of leukaemia are less frequent than the average for the whole of Scotland. Thus, as the authors point out, the influence, if any, of background has to be weighed against other operative factors, such as completeness of case-finding in particular and general social and economic conditions. In fact only about 1% of the increased mortality from leukaemias in Aberdeen could be attributed to the somewhat higher background radiation there, if one accepts the currently

[1] Mole, R. H., *Brit. J. Radiol.*, 1959, **32**, 497.
[2] Phillips, T. A., *Lancet*, 1959, **2**, 659.
[3] Cronkite, E. P., Moloney, W., and Bond, V. P., *Amer. J. Med.*, 1960, **28**, 673.

available figures for relating incidence of leukaemia with radiation-dose received. It therefore seems right to conclude, like the authors, that this radiation played very little part in affecting the recorded incidence. Dr. Eileen Wood has also investigated, in Cornwall, the possibility of a connexion between leukaemia and undue exposure to radiation, whether from radiography during pregnancy or from exceptionally radioactive rock outcrops, and reports her studies in a paper at p. 1760 this week. She could find no significant relationship, and states also that there is no evidence of an increasing incidence of leukaemia in Cornwall since 1948. Moreover, the yardsticks relating radiation to leukaemia are probably not wildly in error—say more than a hundredfold. No doubt they are open to correction; they are based on observation, and can be improved by making more observations. But the importance of this work is that it helps to put into perspective the small part played by natural radiation in the leukaemias, and draws attention to the need, also recently emphasized elsewhere,[3] to investigate more potent causes of the great rise in recorded mortality from this group of diseases during the last 30 years or so in the United Kingdom and other countries with a high standard of living.

HAEMOGLOBIN MOLECULE

Fundamental advances in knowledge of the haemoglobin molecule have been made recently and may later play an important part in medicine. Linus Pauling's[1] demonstration of a difference between the haemoglobin of the normal adult and that of the patient with sickle-cell anaemia has been consolidated by V. M. Ingram's[2 3] finding that the difference consisted only in the substitution of a molecule of glutamic acid for one of valine per half molecule of haemoglobin. Since Pauling's discovery more than twenty molecular variants in haemoglobin have been described on the basis of different physico-chemical behaviour.

W. A. Schroeder[4] has shown that each molecule of adult haemoglobin is composed of two pairs of polypeptide chains. One chain having a valyl–leucyl terminal amino-acid sequence has been labelled the alpha chain, and the second with a valyl–histidyl–leucyl terminal sequence is the beta chain. In foetal haemoglobin two alpha chains are present,[5] but the beta chains are replaced by two polypeptide chains with a glycyl terminal amino-acid; they are referred to as the gamma chains. These chains may be produced by dissociation from the molecule at high or low *p*H. In the adult variants that have been examined the abnormality may be found in either the alpha or the beta chain. Two haemoglobins have been described in which the alpha chains are absent, so that the molecule in this case consists of a tetramer of either the beta chain (haemoglobin H) or the gamma chain (haemoglobin Bart's).

Interest in these polypeptide chains has been heightened by the brilliant work of M. F. Perutz and his team[6] on the elucidation of the size, shape, and internal configuration of horse haemoglobin by use of *x*-ray crystallography. This technique entails the photographic recording of the *x*-ray reflexions from a crystal of haemoglobin while it is being rotated in a beam of *x*-rays. Since these reflexions are brought about by the electrons of the constituent atoms of the molecule, it is possible by mathematical treatment of the recording to determine and plot the regions of high electron density within the molecule.

The results show that the haemoglobin molecule is a spheroid with a length of 64 Å, a width of 55 Å, and a height of 50 Å. In the crystalline state more than half the volume of the crystal is taken up by water of crystallization, which is present in the intermolecular spaces. The positions of the iron atoms are easily recognized because of their high electron density; they are found to lie at the corners of an irregular tetrahedron with distances of 33.4 Å and 36.0 Å between the symmetrically related pairs. The model constructed from the *x*-ray crystallographic data confirms the chemical concept of the haemoglobin being formed of two pairs of different polypeptide chains; it shows that the molecule is indeed formed of four sub-units in two pairs. Both chains are coiled in a similar but not identical fashion, each with a haem molecule fitting into a pocket on the outer surface of the coiled chain. The two pairs of chains fit together in a complementary manner, so that considerable parts of the chains are in close contact.

Though the *x*-ray crystallography was done on horse haemoglobin because of the relative ease of crystallization and the chemical studies were on human haemoglobin, it is not unlikely that the basic molecular plan is the same, with some variation in the constituent amino-acids which may or may not produce an alteration in the contortion of the chains. A similar coiling of the polypeptide has also been detected in sperm-whale myoglobin, where only one chain with one haem molecule is found. Earlier work on this protein has been confirmed by J. C. Kendrew and his group[7] in a companion paper to that of Perutz and colleagues. In handling the large amounts of data obtained in their experiments both groups of workers have used the Edsac Mark II electronic computer of the University of Cambridge.

Such fundamental advances may provide the link in the increasing items of knowledge concerning haemoglobin.

[1] Pauling, L., Itano, H. A., Singer, S. J., and Wells, I. C., *Science*, 1949, **110**, 543.
[2] Ingram, V. M., *Nature* (*Lond.*), 1957, **180**, 326.
[3] See *Brit. med. J.*, 1958, **1**, 1170.
[4] Schroeder, W. A., *Prog. Chem. org. nat. Prod.*, 1959, **17**, 322.
[5] Hunt, J. A., *Nature* (*Lond.*), 1959, **183**, 1373.
[6] Perutz, M. F., Rossmann, M. G., Cullis, A. F., Muirhead, H., Will, G., and North, A. C. T., ibid., 1960, **185**, 416.
[7] Kendrew, J. C., Dickerson, R. E., Strandberg, B. E., Hart, R. G., Davies, D. R., Phillips, D. C., and Shore, V. C., ibid., 1960, **185**, 422.

CEREBROSPINAL FLUID IN INTRACRANIAL TUMOUR

Examination of the cerebrospinal fluid in a case of suspected intracranial tumour carries appreciable risks in view of the frequency with which tentorial or cerebellar herniation may follow lumbar puncture. Nevertheless, when papilloedema and other signs of increased intracranial pressure are lacking, the examination can give information of great diagnostic value. Thus it is well recognized that a rise in the amount of protein in the fluid commonly accompanies many varieties of cerebral tumour. The protein level is particularly high in cases of acoustic neuroma. Furthermore, many tumours, and gliomas in particular, produce a moderate pleocytosis in the fluid, often of about 20 cells per c.mm. These views were amply confirmed in 1958 by M. Locoge and J. N. Cumings[1] in a review of the changes observed in 835 cases of intracranial tumour.

Now W. H. McMenemey and Cumings[2] have gone a step further. In reviewing the cytological and chemical changes discovered in 916 cases of histologically verified intracranial tumour they have paid particular attention to the detailed cytology of the cells which were found in the fluid in some of them. Not only do they tabulate carefully the extent of the pleocytosis and of the rise in protein level which occurred with tumours of different types and in different situations, but they point out that actual tumour cells were identified in the fluid obtained from 17 cases. These cells were recognized in centrifuged deposits of the fluid which were dried rapidly, fixed in methyl alcohol, and stained by Leishman's method. This method had been used only in the past six years, and the authors believe that tumour cells would probably have been recognized in many more cases had similar techniques been employed earlier. Of the 17 cases in which tumour cells were found in the fluid and accurately identified, several were found to be suffering from carcinomatosis of the meninges, but in other patients the presence of tumours as diverse in character as astrocytomas, an oligodendroglioma, a pituitary adenoma, a chordoma, a meningioma, a melanoma, and a myeloma was subsequently confirmed. A. I. Spriggs[3] has previously reported finding tumour cells in the cerebrospinal fluid of 7 personal cases, and he collected a further 66 examples from the literature, of which 47 were of patients suffering from secondary carcinomatosis. Both he and McMenemey and Cumings[2] also stress that in cases of meningeal carcinomatosis the amount of sugar in the cerebrospinal fluid is moderately reduced. This finding can occasionally result in difficulty in distinguishing carcinomatosis from tuberculous meningitis, since the bromide test[4] is often abnormal in both disorders; careful cytological studies should, however, give the answer.

These important observations of McMenemy and Cumings indicate that cytological examination of the cerebrospinal fluid is an important ancillary method which should be employed routinely in investigating those patients suspected of harbouring an intracranial tumour when it appears safe to carry out a lumbar puncture. The method is particularly useful in the recognition of carcinomatosis of the meninges, but occasionally gives diagnostic findings when other types of intracranial tumour are present.

[1] Locoge, M., and Cumings, J. N., *Brit. med. J.*, 1958, **1**, 618.
[2] McMenemey, W. H., and Cumings, J. N., *J. clin. Path.*, 1959, **12**, 400.
[3] Spriggs, A. I., ibid., 1954, **7**, 122.
[4] Smith, H. V., Taylor, L. M., and Hunter, G., *J. Neurol. Neurosurg. Psychiat.*, 1955, **18**, 237.

PREVENTION OF HARM TO PATIENTS

Early last year an anaesthetist who admitted being addicted to inhaled anaesthetics was convicted of the manslaughter of a child who died after an operation.[1] An outcome of this tragic case was a recommendation from the Interdepartmental Committee on Drug Addiction that the responsibility for dealing with an anaesthetist unfortunate enough to develop such an addiction lay with his professional colleagues.[2] The Minister of Health has discussed this problem with the Joint Consultants Committee, and has since issued a memorandum[3] on the subject, the recommendations of which met with the general approval of the representatives attending the recent Conference of Consultants and Specialists (see this week's *Supplement*, p. 355).

How to determine the most appropriate method of dealing with a case of this sort in hospital is best left to the good sense, conscientiousness, and tact of the medical staff, for occasions when the welfare of patients is in any way threatened are extremely rare, and, if they arise, the circumstances will differ greatly from case to case. In its memorandum the Ministry of Health recommends "the setting up by medical staff committees of machinery to assist in preventing harm to patients from physical or mental disability, including addiction, of hospital medical or dental staff." The "machinery" recommended is a small subcommittee of the medical staff committee consisting of three or four members of the senior medical staff "who would receive and take appropriate action on any report of incapacity or failure of responsibility . . . which might, if not remedied, lead to harm or danger to patients."

The memorandum offers fairly detailed guidance on procedure. It suggests that complaints should normally be given orally to the subcommittee or to whichever member of it was most readily available, and that the subcommittee should take steps to verify the accuracy of the complaint. If action is called for, they either "exercise their influence with the individual concerned" or take the matter further by reporting it to the senior administrative medical officer or the secretary of the board of governors.

The memorandum stresses that the subcommittee's responsibilities will be essentially professional, and hospital boards and management committees are urged to rely on them to act appropriately. If any question arises about the subcommittee's activities, then, the

[1] See *Brit. med. J.*, 1959, **1**, 891.
[2] *Drug Addiction. Interim Report of the Interdepartmental Committee*, 1960. H.M.S.O., London.
[3] H.M. (60) 45

memorandum states, it should be referred by the board or committee, before any discussion, to the medical staff committee in the first instance. This is a very necessary admonition in view of what the memorandum calls the "difficulty and delicacy" of the position of medical staff faced with a problem of this sort. Referring to the discussions which preceded the issue of the memorandum, Mr. H. H. Langston told the Conference of Consultants and Specialists that, although the outcome might not satisfy all, it should be a matter of satisfaction that the Ministry of Health had agreed that the control of such delicate matters should be where it rightly belonged—in the hands of hospital medical staff.

THE TRACHOMA VIRUS

The work of S. D. Bell, J. C. Snyder, and E. S. Murray on the virus of trachoma, noted in these columns last year,[1] raised the possibility that trachoma was caused by different strains of virus with different immunity reactions, so that any vaccine eventually produced might have to be polyvalent to be effective. The different strains did, however, show considerable antigenic overlap, so that the differences might not be so formidable as was to be feared. An important study by J. T. Grayston and his associates[2] does in fact justify hopes of producing an effective vaccine. In a remarkably detailed study they carried out in Formosa, they isolated virus in 5 out of 59 cases of trachoma, 4 coming from 34 cases of trachoma stage II, and the fifth from 25 cases of trachoma stage III. They failed to isolate any virus in 11 cases of trachoma stage I. Their studies came from endemic areas where trachoma is relatively mild, and they obtained high titres in 148 children with trachoma II tested with a trachoma antigen. There was a low incidence of high titres in trachoma of the other stages, but that the test was of value is shown by the fact that none of the 11 children with folliculosis gave positive results to complement-fixation tests, and only one child out of 57 with supposedly normal eyes responded in a positive manner. A higher incidence of positive results was obtained in another area of Formosa where trachoma is more severe, and in 8 out of 9 sera supplied from trachomatous children in Egypt. It would appear that there is a real possibility that a skin test for trachoma might be developed. Two results in Formosa with immunization were likewise encouraging, for Taiwan monkeys immunized against trachoma failed to take the infection, though unprotected monkeys of the species respond with a modified trachoma; there was some suggestion of cross-protection against different strains. Of particular interest was their work on man. Six human volunteers inoculated with trachoma virus all became infected. They all showed high titres, but three of the six treated with vaccine during the course of the infection showed both a higher titre and more definite response to treatment. No untoward results have been observed in attempts to vaccinate infants against trachoma, though some of the infants were as young as 2 months. The value of different types of vaccine was tried out in 143 medical and nursing students and it was found that an inactivated vaccine was as effective as a live vaccine, but that the best results were obtained with an aluminium-particle vaccine.

For the moment treatment of trachoma must still be with sulphonamides or the antibiotics. Streptomycin *in vitro* has proved ineffective against the trachoma virus, and chloramphenicol is not very satisfactory. The best results are with penicillin, the tetracyclines, and sulphonamides. The prospects of such treatment becoming modified in the near future are now real, as are the prospects of immunization against trachoma.

[1] *Brit. med. J.*, 1959, **2**, 1014.
[2] Grayston, J. T., Wang, S. P., Woolridge, R. L., Yang, Y. F., and Johnston, P. B., *J. Amer. med. Ass.*, 1960, **172**, 1577.

PROTEIN-LOSING ENTEROPATHIES

A low value for serum albumin is apt to occur in a variety of diseases, some of which are readily recognizable. In malnutrition due to starvation low values are often associated with "famine oedema." In malnutrition due to faulty digestion or absorption of food, such as occurs in pancreatic steatorrhoea and idiopathic steatorrhoea, a similar state of hypoproteinaemia may occur. In the nephrotic syndrome there is heavy loss of albumin in the urine, which is largely, though perhaps not entirely, responsible for the occurrence of oedema. In diffuse inflammatory lesions of the gastro-intestinal tract, such as ulcerative colitis and regional enteritis, hypoproteinaemia can be explained on the basis of exudation of serum from the inflamed surfaces.

Occasionally patients are seen in whom oedema occurs in association with low plasma albumin and in whom no disease is recognizable. Such patients are usually diagnosed as examples of "idiopathic hypoproteinaemia." Deficiency of plasma proteins can occur either because of faulty synthesis or because of excessive loss or destruction. In 1949 F. Albright and colleagues[1] showed in a patient with idiopathic hypoproteinaemia that there was excessive loss of transfused albumin, a finding confirmed by subsequent workers.[2] The term "hypercatabolic hypoproteinaemia" was coined to cover this syndrome, though there was no convincing evidence to distinguish between excessive destruction and excessive loss.

During recent years it has become recognized that at least some of these patients lose excessive amounts of albumin into the gastro-intestinal tract. Some albumin always enters the lumen of the small intestine, where it is digested and the products are reabsorbed. In the patients now being discussed the rate of loss of protein is much higher than normal and appears to exceed the rate at which new albumin can be synthesized by the liver. In some of these patients careful search will reveal an inflammatory lesion of the gastro-intestinal

[1] Albright, F., Bartter, F. C., and Forbes, A. P., *Trans. Ass. Amer. Physns*, 1949, **62**, 204.
[2] Schwartz, M., and Thomsen, B., *Brit. med. J.*, 1957, **1**, 14.
[3] Holman, H., Nickel, W. F., and Sleisenger, M. H., *Amer. J. Med.*, 1959, **27**, 963.
[4] Schwartz, M., and Jarnum, S., *Lancet*, 1959, **1**, 327.
[5] Gordon, R. S., Jr., *J. polym. Sci.*, 1958, **31**, 191.
[6] —— *Lancet*, 1959, **1**, 325.

tract which can be held responsible for the abnormality, but in others no organic lesion is detectable, at any rate by the methods normally used in clinical medicine, for some considerable time after the onset of oedema.

H. Holman and colleagues[3] have recently published an account of six patients in three of whom hypoproteinaemia appeared before any evidence of intestinal disease could be found. When these patients were given intravenously albumin and γ-globulin labelled with radioactive iodine, it was found that these substances were rapidly lost from the plasma. The authors infer that the rapid loss was due to excessive passage of plasma proteins into the intestine. Their view is supported by a number of other studies, which have been reviewed by M. Schwartz and S. Jarnum.[4] Further evidence comes from the work of R. S. Gordon, who has developed a most ingenious technique.[5,6] Gordon has used radioiodinated polyvinylpyrrolidone (P.V.P.), which has a similar molecular weight to albumin but differs from it in not being digested by the enzymes of the intestinal tract. Hence, when this substance enters the gastro-intestinal tract it is excreted in the faeces and a quantitative estimate is readily made. By injecting a standard dose intravenously, the amount of the substance appearing in the faeces can easily be compared with the amount appearing in normal subjects. In nine subjects with the characteristics of "idiopathic hypoproteinaemia" thus studied, Gordon found that the rates of loss of the P.V.P. into the gastro-intestinal tract were higher than normal in all of them. In four of the subjects no abnormality of the gastro-intestinal tract was found, while the remaining five showed minor, non-specific changes.

The importance of these studies is twofold. On the one hand, when a patient presents with oedema and there is no obvious cause, such as renal disease, to account for it, the gastro-intestinal tract should be investigated with great care. If no lesion is found, the patient should be kept under supervision and reinvestigated from time to time so that any underlying lesion, such as giant hypertrophic gastritis, regional enteritis, or ulcerative colitis, can be recognized as early as possible and treated appropriately. On the other hand, it appears possible that some of these cases of "protein-losing enteropathy" may represent a previously unrecognized condition in which the gastro-intestinal mucosa is abnormally permeable to plasma albumin in the absence of gross structural organic disease. It is a subject which promises to advance in the next few years.

B.M.A.'S AUTUMN MEETING

The Annual Clinical Meeting of the B.M.A. this year is to be held at Middlesbrough, Yorkshire, on October 6–9, and the provisional programme is published in the *Supplement* this week (p. 353). It offers a variety of attractions in the form of clinical discussions and demonstrations, televised operations, a trans-atlantic conference on endocrinological cases, and visits to I.C.I.'s factories to see something of industrial medicine. In addition some lighter diversions will be arranged. Visitors to the meeting will certainly enjoy not only the fare offered in the programme but equally the warm hospitality for which the North of England is famous. Close by is the beautiful scenery of Teesdale, with its unique flora, and the North Yorkshire moors.

WELLCOME TRUST REVERSES THE TIDE

For the most part the tide of charitable benefactions flows across the Atlantic in an easterly stream. Every now and again the direction is reversed, with a consequent boost to European morale. This week the Wellcome Trustees in London made a grant of £50,000 (approximately $140,000) to the Massachusetts General Hospital, Boston, for the establishment of a Henry S. Wellcome research chair in medical science. The professor will be chosen by a special committee of the Massachusetts General Hospital, Harvard University, and the Massachusetts Institute of Technology, and the appointment will be for 10 years.

This is not the first grant made by the Wellcome Trustees to a medical research centre in the United States, but it is the largest. Many British medical graduates have greatly profited from study at the Massachusetts General Hospital, which will be celebrating its 150th anniversary next year, and they in particular will be glad that the Wellcome Trustees have chosen this famous institution for a major grant.

FRENCH DOCTORS STRIKE

The "administrative strike" of French doctors against certain measures proposed by those in charge of the health insurance scheme has gathered force. The dispute between the Government and the French medical profession is the subject of an article in this week's *Supplement* by Dr. M. Poumailloux, of Paris, who is the European secretary of the World Medical Association. Both the Ordre des Médecins (to which all French doctors have to belong) and the Confédération des Syndicats Médicaux Français (membership of which is voluntary) support this action decided upon by our French colleagues. And they are powerfully backed up by the Faculty of Medicine in Paris under the leadership of that great man of letters, Dr. Georges Duhamel. It is not easy for the British doctor unfamiliar with the provision of medical services under the French *Sécurité Sociale* to follow the details of the present dispute. But, as Dr. Poumailloux points out, the "administrative strike" has started and spread because the French medical profession "will not be forced to sign agreements without being in a position to discuss all the details which, upon examination, infringe the independence and the liberal character of the profession."

We record with regret the death on June 3 of Sir Henry Tidy, K.B.E., Extra Physician to the Queen and consulting physician to St. Thomas's Hospital.

Drug Treatment of Disease

VASODILATOR DRUGS FOR PERIPHERAL VASCULAR DISEASE

BY

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INTRODUCTION

The number and complexity of drugs which are capable of producing peripheral vasodilatation are inversely related to their value in the treatment of peripheral vascular disease. More precise knowledge of the disorders of function and of anatomy of the peripheral vascular system has emphasized the importance of reconstructive surgical treatment and outlined the deficiencies in medical methods of treatment. Enthusiasm for vasodilator drugs has waned appreciably, and it has even been suggested that such drugs may actually impair rather than improve the blood flow to ischaemic limbs (Gillespie, 1959). The time is therefore ripe for a critical appraisal of the place and value of vasodilator drugs in the treatment of peripheral vascular disorders.

VASODILATOR DRUGS

Tone is maintained in the peripheral blood vessels, particularly in those of the skin, by adrenergic stimulation. Vasodilatation can be produced by interrupting sympathetic vasoconstrictor nerve impulses or by a local action on the vessel wall.

Thus drugs may act centrally; by ganglion-blockade; by blocking vasoconstrictor impulses; by neutralizing or reversing the action of adrenaline; or by a direct action on the vessel wall. Many substances combine more than one action and are extremely complex in their effects.

Central Action

Drugs in this group exert a sedative and depressant action on the central nervous system, including the vasomotor centre, and produce some central inhibitory effect on sympathetic tone. Reserpine, an ester-alkaloid from the root of certain species of *Rauwolfia*, has a depressant and hypotensive action, but produces only very slight peripheral vasodilatation. Chlorpromazine hydrochloride and promazine hydrochloride are phenothiazine derivatives which produce central nervous depression, and in this way may cause some dilatation of blood vessels. In addition, they also have adrenolytic and antispasmodic actions. In general, however, drugs with a central action have only a very weak peripheral vasodilating effect, and are not used for this purpose.

Ganglion-blocking Action

These drugs interrupt adrenergic impulses at the level of the autonomic ganglia. Their chief use is in the treatment of hypertension, but they also cause peripheral vasodilatation. Examples in this group are hexamethonium, pentolinium, mecamylamine, pempidine, and chlorisondamine. They are, however, unsuitable for routine use because of their hypotensive effects, and because of side actions which are due mainly to associated parasympathetic blockade. Hamilton *et al.* (1954) have shown that an appreciable increase in limb blood flow can be produced by an injection of hexamethonium.

Adrenergic Blocking Action

These substances produce vasodilatation by preventing or reversing the peripheral effects of adrenaline. The terms adrenergic blocking, adrenolytic, and sympatholytic are often used synonymously. A sympatholytic drug must, of course, be also adrenolytic, though the reverse is not necessarily the case. Drugs in this group are tolazoline (imidazoline, "priscol"), phentolamine ("rogitine"), phenoxybenzamine ("dibenyline") (Wertheimer *et al.*, 1954), azapetine ("ilidar") (Green and DuBose, 1954) and a new substance recently marketed under the name of "vasculit" (Duff, 1959). These drugs act mainly on small peripheral arteries, and thus do not greatly lower blood-pressure.

The new hypotensive agent, bretylium tosylate, has a selective paralytic action on the peripheral adrenergic neurones (Boura *et al.*, 1959). As yet it has been used only for the treatment of hypertension, and the objections to the ganglion-blocking agents also apply to bretylium in the treatment of peripheral vascular disease. Chlorpromazine and promazine, in addition to central depressive effects, also have an adrenolytic action. Dihydroergocornine, a dihydrogenated derivative of ergot, reverses the vasoconstrictor action of adrenaline without producing a direct constrictor effect on the vessel wall. It is also sympatholytic and has a central depressant action. It has been used to lower blood-pressure and also may produce peripheral vasodilatation (Goetz, 1949; Goetz and Katz, 1949).

Direct Action on Blood Vessel Wall

In this group are the nitrites, papaverine, alcohol, β-pyridyl carbinol ("ronicol"), and procaine.

THE VASODILATOR PARADOX

The object of using any vasodilator drug or medical method in the treatment of peripheral vascular disease is to produce selective and sustained vasodilatation in an ischaemic limb. This effect must not be achieved at the expense of producing generalized vasodilation throughout the body, which would lower blood-pressure and might actually reduce the perfusion to the affected limb. If this occurs, then it might be argued that the blood flow to the ischaemic part would actually fall rather than increase. The ideal vasodilator drug would be one which produces a marked vasodilating effect restricted to the ischaemic part. Such a drug should produce an effect similar to selective sympathectomy, which is the best method (other than arterial reconstruction) of increasing the blood flow to an ischaemic limb. There is, however, no drug which will restrict its effects merely to one limb, and therefore the more effective the vasodilator the more widespread and marked will be the vasodilatation and the less the effect in the ischaemic part. It is this difficulty which is mainly

responsible for the failure of vasodilators in peripheral vascular disease, for there is no doubt that many drugs will significantly increase the blood flow in a normal limb.

It is the practical experience of most workers in the field of peripheral vascular disease that vasodilator drugs are of only very limited value. Gillespie (1959) has produced evidence to suggest that these drugs are actually harmful, for by measuring blood flow to the limb by venous-occlusion plethysmography he showed that in the healthy limb a blood flow of up to 500% could be obtained after the intravenous injection of a vasodilator drug. However, in the abnormal limb, blood flow could actually fall for the reasons which have already been outlined. His conclusions that vasodilators have no place in the treatment of acute or chronic arterial occlusion are perhaps too sweeping, however, for there is evidence that vasodilating drugs, by mouth or by injection, are capable of producing increased blood flow in diseased limbs, when measured objectively.

Grimson *et al.* (1948) produced an increase in skin temperature in the affected extremities of patients suffering from Raynaud's phenomenon and thrombo-angiitis obliterans by the administration of tolazoline by mouth. Lynn (1950) noted that tolazoline acted mainly on the skin vessels, producing an increase in blood flow to the hands and feet in patients with Raynaud's phenomenon and with occlusive arterial disease. He also showed that intravenous injection had no effect on the sympathectomized limb, whereas intra-arterial injection almost doubled the calf blood flow to that limb, indicating that tolazoline also had a dilator effect on the vessel wall in addition to its adrenergic blocking action. Goodwin and Kaplan (1951) showed that tolazoline by mouth increased the skin blood flow to ischaemic limbs, the flow returning to pre-treatment level after discontinuing the drug. Similar results have been reported with phentolamine, phenoxybenzamine, and azapetine. Many of the reports, however, are difficult to assess owing to lack of quantitative objective evidence of improvement in the circulation.

Improvement in the circulation after a long period of time is often due to the development of collateral vessels rather than to any drug, and it is exceptional for any vasodilator drug to have any very distinct and lasting effect in occlusive peripheral vascular disease. In Goodwin and Kaplan's (1951) series the objective evidence of increase in blood flow as a result of tolazoline was convincing, but the amount of improvement gained by the patients was limited, presumably owing to the progressive nature of the occlusive disease. It is now recognized that in patients with signs of ischaemia of a limb with or without intermittent claudication an arterial block is almost invariably present. This situation is likely to limit the effects of vasodilator drugs, and focuses attention on the importance of reconstructive surgery to restore an adequate blood supply to the limb.

INDICATIONS FOR TREATMENT WITH VASODILATOR DRUGS

Vasospastic Disorders

Conditions characterized by episodic hypertonus of digital blood vessels, such as Raynaud's disease, are commonly treated with vasodilator drugs, but with only moderate success. In primary Raynaud's disease the digital arteries are unduly sensitive to cold and develop acute spasm on exposure to low temperatures. Treatment with one of the adrenergic blocking drugs such as tolazoline, phentolamine, or phenoxybenzamine is rational, especially in the winter. It should be combined with measures to keep the hands and feet warm by wrapping them up well and avoiding exposure to cold so far as possible.

Raynaud's phenomenon, however, is often a sign of more serious organic disease of the vessels, and may be a feature of thromboangiitis obliterans, scleroderma, or systemic lupus. Furthermore, it may be produced by local conditions such as a cervical rib or thoracic-inlet syndrome, or be associated with cold agglutinins or cryoglobulins. It is therefore important to make sure that no underlying condition requiring other treatment is present. Secondary Raynaud's phenomenon may be associated with digital thrombosis, and this may account for some failures with vasodilator drugs.

Vasodilators may be of some value in the treatment of chilblains, though this is somewhat questionable.

Chronic Occlusive Arterial Disease

In these cases vasodilator drugs should be given only in addition to surgical treatment or when surgical treatment is impossible because of generalized vascular or other disease. One or more of the adrenergic blocking drugs may be combined with reflex heating in patients with chronic gangrene or with threatened gangrene. The dosage of the various drugs is indicated in Table I. In general the intramuscular or intravenous routes have little superiority over the oral route, which is of course much simpler. Repeated intra-arterial injections have been advocated but are now losing favour. Edwards *et al.* (1952) reported on the results of repeated intra-arterial injections into ischaemic limbs of tolazoline, papaverine, alcohol, acetylcholine, and histamine. Nine patients were apparently considerably improved after several arterial injections of one or other of these substances. However, Catchpole and Jepson (1954) reported that the increase in blood flow produced by intra-arterial injection was disappointingly transient, and were sceptical of the value of such treatment.

If vasodilator drugs are to be given orally they should be given in the maximum tolerated doses. It is possible to combine more than one drug, though evidence of synergism is lacking. Patients, however, may tolerate one drug rather than another and so it is worth trying several until the most satisfactory one has been found.

One of the most satisfactory vasodilators is alcohol. One or two ounces of whisky or brandy last thing at night will produce not only gentle vasodilatation but also satisfactory sleep. This is a valuable form of treatment in elderly patients with occlusive vascular disease and should not be neglected in favour of esoteric modern drugs.

The most distressing feature of severe peripheral vascular disease is ischaemic pain at rest, which is often an indication for amputation, and many patients endure great misery before this is carried out. Vasodilators are of little value in the relief of this pain, but some improvement may sometimes be obtained by raising the head of the bed at night, and by giving alcohol and a sedative such as promazine, which perhaps has some

TABLE I.—*Some Drugs Other Than Alcohol Which May Be Used for the Induction of Peripheral Vasodilatation*

Drug	Site of Action	Hypotensive Effect	Side-effects	Usual Daily Oral Dose (mg.)	
				Initial	Maximum
Tolazoline (priscol) ..	Sympatholytic and local. Mainly acts on digital vessels	Slight or absent, except in high dosage	Palpitation, goose-flesh, dyspepsia, headache	75	400
Phentolamine (rogitine)	,, ,, ,,	,, ,, ,,	,, ,, ,,	75	400
Phenoxybenzamine (dibenyline)	Adrenergic blockade	,, ,, ,,	Nasal congestion, miosis, drowsiness, tachycardia, dry mouth, wheezing	20	120
Azapetine (ilidar) ..	Adrenergic blockade and local action	,, ,, ,,	Dyspepsia, weakness, dry mouth, nasal congestion, headache, palpitation	75	300
"Vasculit"	Sympatholytic	? Absent	Possibly less than other related drugs	25	100
β-Pyridyl carbinol (ronicol)	Local	Negligible	Flushing	200	400

vasodilating action in addition to its tranquillizing effects. Alternatively, methylpentynol ("oblivon") or trifluoperazine ("stelazine") may be of value, and are safer. Methylpentynol, one of the higher alcohols, may be given in a dose of 1 g. at night, or as the carbamate 200 mg. 2–5 times daily. But often stronger drugs are required and morphine or pethidine may be necessary. The risks of addiction from opiates and of serious toxic effects from promazine or chlorpromazine, such as bone-marrow depression or liver damage, may have to be run in order to relieve the intolerable pain. Misplaced faith in vasodilating drugs should not delay reconstructive surgery or amputation.

Peripheral Arterial Embolism

Embolism to a major artery is a medical emergency. The most important therapeutic measures are the relief of pain, the use of heparin to prevent spread of the embolus, and the control of cardiac arrhythmia and congestive heart failure if present. Early consultation should be held with the vascular surgeon lest embolectomy be required. Vasodilatation in the ischaemic limb is encouraged by exposing the limb to the air and warming the trunk.

Vasodilator drugs have only a small part to play in the treatment of embolism. The injection of a vasodilator substance into the artery proximal to the obstruction is sometimes practised and may have some limited value in certain cases, though enthusiasm for its use is now waning. If it is desired to give an intra-arterial injection—for example, into the femoral artery—tolazoline is probably the most satisfactory drug to use; 25–50 mg. diluted in 10 ml. of saline may be slowly injected into the artery. Firm pressure over the artery must be applied for at least five minutes after the puncture to prevent a haematoma. This is particularly important if the heparin has already been given, lest a very large haematoma result.

It is doubtful whether the effects of intra-arterial injection are sufficiently sustained to be of much value, but tolazoline or other drugs of the same group may be given by intramuscular injection or by mouth (Table I). However, perhaps the best vasodilator in these circumstances is alcohol by mouth.

Procaine paravertebral nerve block to simulate the effects of sympathectomy has little to recommend it. On no account should protracted treatment with vasodilators delay embolectomy in cases where this operation is necessary. The results of treatment of serious arterial embolism are poor (Martin, 1959; Jacobs, 1959). They are likely to become even worse if those patients whose limbs might be saved by operation are denied this because of misdirected "vasodilator" treatment.

Intermittent Claudication

The increased blood flow to skeletal muscles which normally occurs on exercise is due to the accumulation of local metabolites which are powerful vasodilators. Such vasodilatation is not apparently under the control of the autonomic nervous system. It is therefore improbable that any vasodilator drug will be capable of increasing blood supply to claudicating muscles sufficiently to relieve pain. This in fact is the case.

Hamilton and Wilson (1952) in a carefully controlled trial showed that none of the vasodilating drugs had any significant effect upon intermittent claudication. The same, of course, applies to sympathectomy, which does not increase blood flow to muscles. Although there is good experimental evidence that adrenaline will increase blood flow to muscles (Barcroft and Swan, 1953), Hamilton and Wilson (1952) did not find that subcutaneous injections of adrenaline had any effect on the duration or severity of intermittent claudication. The assessment of severity of intermittent claudication based on exercise tests at different times is notoriously fallacious. Improvement after certain drugs is probably due to the natural improvement in the disease or reduction in pain sensitivity which commonly occurs without any treatment at all.

At the present time there is no drug treatment for intermittent claudication other than the administration of haematinic substances to correct anaemia if present. Persistent indulgence in expensive vasodilators is to be deprecated, for the treatment of intermittent claudication due to arterial obstruction is essentially surgical. This is not to say that patients with intermittent claudication should never be treated with vasodilators. Many of them have ischaemia of the skin, which may be improved to some extent by the use of certain vasodilating drugs, but it should be clearly understood that these drugs are given to improve blood flow to the skin and not claudication.

CHOICE OF VASODILATOR DRUG

Table I lists the drugs which may be used for producing peripheral vasodilatation. Personal experience suggests that the most useful are tolazoline, phentolamine and phenoxybenzamine. These and azopetine are best given by mouth. The dosages are set out in Table I. Their duration of action is 4–6 hours.

with the exception of phenoxybenzamine, which acts for up to 12 hours, and need be given only twice a day; there may also be a delay of up to two weeks before it produces any definite effect. If necessary administration by mouth may be supplemented by intramuscular injection, but in general this does not seem to have great superiority. There is little point in giving the drugs intravenously, unless a very rapid action is desired. The initial dose by injection should not exceed 25 mg. of tolazoline or phentolamine. "Vasculit" can produce appreciable vasodilatation without hypotension when given by injection (Duff, 1959).

β-Pyridyl carbinol is the alcohol of nicotinic acid. Its action on blood vessels is purely local and it is of little clinical value, though it may be used to enhance the action of a sympatholytic drug. Papaverine has no appreciable vasodilator action except when applied directly to the arterial wall. Alcohol has already been mentioned as a useful vasodilator. The nitrites are of no value in producing peripheral vasodilatation.

TOXIC EFFECTS AND DANGERS

The adrenergic blocking agents are complex substances capable of producing unpleasant side-effects. Most of these are due either to hypotension or to adrenergic blockade. Thus faintness, vertigo, headache, sweating, and "goose-flesh" may all result, particularly from parenteral administration. These side-effects may limit the use of the drug. More serious consequences of adrenergic blockade may be peptic ulceration, or perforation of an existing ulcer. Vomiting or diarrhoea may occasionally occur. The gastric effects, however, can usually be minimized by giving at the same time a non-absorbable antacid such as aluminium hydroxide. If it is considered desirable to administer tolazoline to a patient with a history of dyspepsia, an antacid should always be given in addition.

Cardiac infarction has been reported in patients taking tolazoline, but there is no certain evidence that the drug has been responsible for this complication, the infarction probably resulting from the associated occlusive coronary artery disease which so commonly complicates peripheral vascular disease. However, it should be remembered that tolazoline has extremely complex actions in animals, consisting of histamine- and acetylcholine-like properties as well as sympatholytic and local actions on blood vessels. Thus coronary vasoconstriction, bradycardia, and stimulation of the gut have been reported in rabbits receiving the drug (Ahlquist *et al.*, 1947).

The administration of adrenergic blocking drugs to patients subject to asthma may precipitate an attack of bronchospasm, and this possibility should always be borne in mind before administering one of them. In practice, however, the side-effects from the usual dosage are seldom serious.

CONCLUSION

There is a limited place for the use of vasodilator drugs in the treatment of vasospastic disorders such as Raynaud's phenomenon and to supplement other methods of medical treatment such as reflex heating, sedation, and anticoagulant therapy in acute and chronic occlusive arterial disease. When reconstructive arterial surgery is not practicable, sympathectomy is the best method of producing a sustained increase in blood flow to the skin of the ischaemic limb. Once again it should be emphasized that correct surgical treatment should never be denied because of unrealistic faith in vasodilator drugs.

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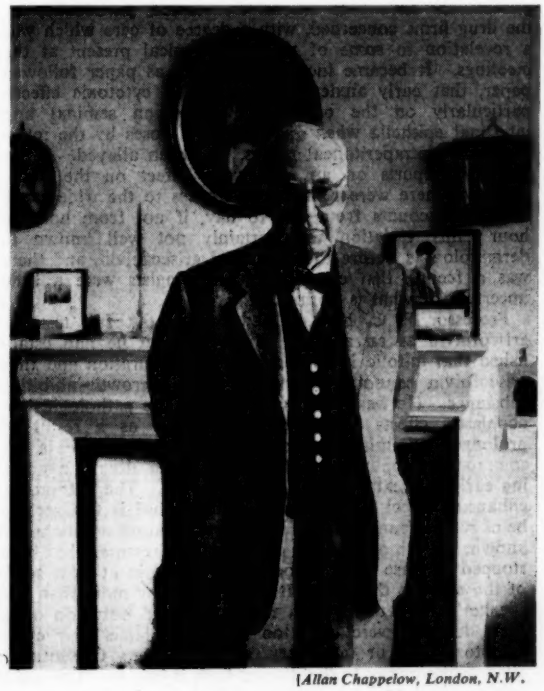
SIR HENRY DALE, O.M., 85

Doctors the world over will wish to join with us in extending affectionate greetings to Sir Henry Dale on the occasion of his 85th birthday, celebrated on June 9. The photograph reproduced here was taken at his home a week or two ago. It is the portrait of a man who, as Lord Adrian wrote in this journal five years ago, has "helped to guide the whole course of scientific work in Great Britain" as head of the National Institute for Medical Research and President of the Royal Society.



[*Allan Chappelow, London, N.W.*

He is still as active as ever in presiding over the beneficent work of the Wellcome Trust and in giving friendly and shrewd counsel to his colleagues, whether working in the laboratory or by the bedside. He has indeed lived to see the fulfilment of his dream, the application by the clinical worker of the experimental method to the elucidation and control of disease.

SYMPOSIUM ON GRISEOFULVIN

[FROM A SPECIAL CORRESPONDENT]

The coming of age of griseofulvin—for it was first isolated by Oxford and his colleagues in 1939—was celebrated by the holding of an international symposium at the Royal Society of Medicine on May 13 and 14 under the wing of the St. John's Hospital Dermatological Society. It is, of course, only some eighteen months since the first clinical trials of the drug were begun. It was hailed with wild excitement in some countries, but with studied calm and some healthy disbelief in this. The time had come, it was felt, for the status of this promising youngster to be discussed.

Dr. A. H. CAMPBELL described the development of large-scale production of griseofulvin and methods of improving the yield. Early hopes that it might be the answer to fungal diseases of plants, Dr. P. W. BRIAN reported, have been disappointed, partly because of its cost and partly because it is no better than established fungicides. In the veterinary field there seems to be room still for experiment and for argument. Miss O. UVAROV and Dr. C. J. LATOUCHE pleaded eloquently for as much compassion for infected animals as is given to infected humans.

Toxicity and Side-effects

The pharmacological properties and the toxicity of griseofulvin have been extensively studied, particularly by the drug firms concerned, with a degree of care which was a revelation to some of the more cynical present at the meetings. It became increasingly clear, as paper followed paper, that early anxiety because of its cytotoxic effects, particularly on the bone-marrow and on seminal and intestinal epithelia when given in large doses by the intravenous or intraperitoneal routes, had been allayed. There were no reports on any important effect on the bone-marrow: there were repeated references to the wide range of normal counts from day to day, if not from hour to hour; this variation was certainly not well known to dermatologists before the advent of griseofulvin, and there was a feeling that even the haematologists were a little uncertain of what is normal.

Professor P. C. KOLLER had carried out full tests of griseofulvin as an arrester of mitosis, but he had established that mitotic inhibition is of short duration and thus griseofulvin cannot be considered as a growth-inhibiting substance. He was also unable to produce pathological or neoplastic effects locally or systemically as a result of prolonged administration of the drug. Headache is the commonest symptom caused by griseofulvin, usually happening early in treatment and soon stopping. The entrancing, enhancing effect of griseofulvin on alcohol is too rare to be of real account. Urticaria and erythematous eruptions are known, as with almost any other drug. Treatment has been stopped because of diarrhoea attributable in at least some of the cases to the drug. It was stressed by more than one speaker that patients on a new drug—and only too often their doctors—were only too ready to blame their every symptom, real or imaginary, on that drug. Griseofulvin gives no immunity to the ills our flesh is heir to. This point was emphasized by a controlled trial described by Dr. W. FRAIN-BELL in which an equal number of side-effects, including rashes and diarrhoea, occurred in patients on griseofulvin and on dummy tablets. Griseofulvin, it was generally agreed, is a preparation singularly free of toxic effects. No serious trouble has yet been reported and over a million patients have been treated, many continuously for very many months.

Clinical Administration

Most speakers on the clinical aspects had treated their patients with a daily dose of one gramme, as initially recommended after animal work. There is no evidence whether this is better given in single or in divided doses. Theoretically a single dose might suffice for cure as long as there was no reinfection behind the advancing wave of griseofulvin and as long as the drug remains active throughout its life in keratin. It was pointed out, of course, that it has not been possible as yet to prove that the fungistatic substance present in keratin is in fact griseofulvin or a breakdown substance. While a single dose has been shown to be effective in the treatment of infections of relatively fast-growing structures such as hair, it was the general experience that short courses of treatment, or erratic treatment, were doomed to failure. On the other hand, for such sites as the nails, where growth is slow and treatment long, two grammes twice a week seems quite adequate. Cure cannot be accepted nor indeed expected in any tissue until the last remnant of infected hair, nail, or scale is shed or mechanically removed.

Clearly the greatest importance of the drug is in the treatment of ringworm of the scalp, which, as Dr. R. H. MEARA, from London, Dr. J. MARTIN BEARE, from Belfast, and Dr. E. RIVALIER, from Paris, pointed out, rarely fails to respond to the first course of treatment. Failure to respond or reinfection can be cured by further griseofulvin. Resistance *in vivo* has not yet been shown to exist. Removal of the infected parts of the hairs, when they have grown away from the scalp, is essential; this is done by shaving or clipping at about three weeks. Where the extent of the infection can be observed under Wood's light, as in the small-spore infections, only the diseased area need be clipped. In the other cases the whole scalp must be so treated. Frequent shampooing and the use of an antifungal preparation are necessary to prevent later reinfection, and are continued for a week or two after griseofulvin has been stopped. Reinfection from brushes, caps, and the like can still occur.

Ringworm of the body has rarely been a problem except for favus, Tokelau ringworm of the South Seas, and certain cases of *Trichophyton rubrum* infection. These all get well with relative ease in about a month.

There seem to have been few failures to cure fungous infections of finger-nails, although this takes as long as the growth of a nail—that is to say, six months. Interest has shifted to the possibility of reinfection; will those people prone to catch fungous infections go on doing so every time they have been cured? Avulsion of nails combined with griseofulvin by mouth is a more certain and quicker route to cure. Toe-nails remain a considerable problem. It was agreed that even after more than a year of treatment only a very small percentage could even be suspected of being cured!

Athlete's Foot

What of athlete's foot? There was no doubt that the ordinary blistery eruption of the soles, whatever the infecting fungus, could be cured in about four weeks, the time taken for the last shred of scale to be shed. There are locally applied preparations which will do as well. On the other hand, diffusely hyperkeratotic soles, usually associated with a *Trichophyton rubrum* infection, have long been a therapeutic headache. While griseofulvin seems to cure many of these, undoubted failures are seen and a surprising number of cases show gross evidence of relapse even when they are still taking griseofulvin. It remains a mystery why a drug which can apparently remove infection from the

nails, palms, and soles of a patient seems incapable of affecting the course of the same infection in his clefts. No large-scale trial has been reported of the treatment of pure "foot rot" with no infection in other areas. Although Dr. A. SCOTT showed from auto-radiographic studies that griseofulvin can be absorbed even into the keratin of the palms, there is no satisfactory clinical evidence that a combination of oral and local griseofulvin will cure the difficult cases.

Since it is evident that the cure rate is high, although it may sometimes be difficult to be sure of cure in certain types of case, interest is now shifting to the questions of reinfection, possible development of immunity, and the mystery of the clefts which refuse to get well. The situation may well be complicated by the development of more powerful analogues; but, as one speaker said, there are no classic fillies in the field yet.

PLATELET PHYSIOLOGY AND PATHOLOGY

[FROM A SPECIAL CORRESPONDENT]

An international symposium on the blood platelets was held at the Henry Ford Hospital, Detroit, on March 17, 18, and 19, at which papers were read by 51 invited participants. The first day was devoted to papers on the role of platelets in haemostasis and thrombosis.

Haemostasis and Thrombosis

Dr. G. P. FULTON, of Boston, used colour film to demonstrate the aggregation of platelets in damaged blood-vessels, and described the variation of stimulus needed to produce aggregation in various induced states. Dr. JENO KRAMIR, of Omaha, stated that the degree of capillary resistance was relatively constant for the individual, though emotion or cortisone could increase it, and the absence of platelets or administration of heparin tended to diminish it. Dr. W. O. CRUZ, of Rio de Janeiro, gave a detailed account of his perfusion experiments and their effect on haemostasis in the hind leg of a dog. Contrary to most other speakers, he believes that platelets play a minor role in haemostasis and that plasma contains the major haemostatic components. Homologous arterial blood was haemostatic, while venous blood was not. Oxygenation did not confer haemostatic properties on venous blood, but he found that the addition of phosphatidyl ethanolamine did. *In vivo* experiments showed that chyle from the thoracic duct and passage through lungs were both essential to confer haemostatic activity on venous blood. Plasma lipoproteins were, in his opinion, the haemostatic component of the plasma.

Dr. A. A. SHARP, of Oxford, described the sequence of platelet metamorphosis in normal blood and in blood derived from patients with haemorrhagic disorders. From the pattern of results obtained he concluded that platelet viscous metamorphosis in clotting blood evolves in two stages: (1) aggregation—a reversible state induced by a tissue factor; and (2) fusion—a permanent state induced by thrombin. These observations and their relationship to the mechanisms of haemostasis and thrombosis were discussed. Dr. K. M. BINKHOUSE, of Chapel Hill, described the properties of the thrombocyte agglutinating factor in plasma. This appears to be a separate plasma factor unrelated to any known plasma coagulation factor. Dr. L. B. JAQUES, of Saskatoon, reviewed the importance of multiple factors in the causation of spontaneous haemorrhage. He found that while one factor, such as heparin, did not cause spontaneous bleeding in an animal, the addition of another, such as stress, induced a severe haemorrhagic state.

The role of fat and platelets in the pathogenesis of thrombosis was discussed by Dr. W. THOMAS, of New York, and Dr. J. F. MUSTARD, of Toronto. The former described how a butter-cholesterol diet in conjunction with lard produced a high incidence of cardiac infarction in rats. Dr. MUSTARD claimed that in humans a lipoid meal induced increased platelet adhesiveness and shortened platelet-survival in the circulation.

Platelet Chemistry

The chemistry of platelet function was discussed during the second day of the symposium. Dr. W. H. SEEGERS, of Detroit, described how platelet factor III activity could alter purified prothrombin to autoprothrombin I and in conjunction with other coagulation factors to thrombin. Dr. D. M. SURGENOR discussed the biophysics of platelet mechanisms in clotting. Basing his argument on studies of the strong platelet-like activity of egg phosphatidyl ethanolamine in clotting plasma, he described how this clot-promoting activity was a property of particles in colloidal suspension. The activity depended on the degree of unsaturation of the fatty acids in this phospholipoid and on the temperature, *p*H, and ionic strength of the suspending medium. The behaviour of the phosphatidyl ethanolamine in the systems studied suggested they exist as micelles of bimolecular leaflets of limited size, thickness, and surface configuration. Dr. NORMA ALKJAERSIG, of St. Louis, demonstrated that platelets in concentrated suspensions could inhibit fibrinolysis but had little effect in physiological concentrations. Dr. E. DEUTSCH, of Vienna, defined the chemical properties of platelet factor IV (anti-heparin), which is a separate and well-defined fraction of platelet extracts.

Dr. G. V. R. BORN, of Oxford, gave an account of the work performed by Mr. M. P. ESNOUF and himself on the breakdown of phosphorus components in platelets and plasma during clotting. The high concentration of adenosine triphosphate in the platelets rapidly disappeared in clotting plasma and did not appear in serum; this could not be accounted for on the basis of conversion to adenosine monophosphate or diphosphate. As platelet-rich plasma clotted there was an increase of inorganic phosphate and a rapid breakdown of a small proportion of plasma lecithin to glyceryl phosphoryl choline. Dr. R. GROSS, of Marburg, in studies of the glycolytic cycle in the platelets had discovered that abnormal platelet function is related to a deficiency of the enzyme glyceraldehyde-3-phosphate dehydrogenase.

Clot Retraction

The role of platelets in clot retraction was defined by Dr. C. L. CONLEY, of Baltimore, and Dr. E. F. LUSCHER, of Berne, Switzerland. The latter described how he had isolated from platelets a protein which could be made to contract by the addition of adenosine triphosphate. This protein had similar properties to the actomycin of muscle.

Platelet Transfusions

The ability of transfused platelets to induce normal haemostatic function in the thrombocytopenic patient was discussed by Dr. D. P. JACKSON, of Baltimore, and Dr. F. H. GARDNER, of Boston. Only fresh platelets were haemostatic, and freeze-dried or otherwise disintegrated platelets had no such activity. The moment platelets were added to an anticoagulant the yield of platelets dropped to 60–70% and platelets over 4–8 hours old were no longer efficient in promoting haemostasis. The best method of performing platelet transfusion was vein-to-vein transfusion with siliconized equipment. Platelet concentrates must be used within 3 hours to be effective. The preservation of platelets by freezing in glycerol-dextrose solution was possible, but the yield was reduced to 30–40% and the survival of these platelets in the recipient was also reduced.

Abnormal Platelet Function

Abnormal platelet function in haemorrhagic states was discussed, and Dr. B. ALEXANDER, of Boston, described how altered function might precede the development of thrombocytopenia, and suggested that thrombocytopenic bleeding might be the result of qualitative as well as a quantitative

defect. Dr. S. A. JOHNSON, of Detroit, and Dr. O. N. ULUTIN, of Istanbul, discussed the relationship of the platelet thromboplastin component (platelet factor III) to altered haemostatic function. While certain cases showed quantitative deficiency of this factor, in others there was only a failure to release this substance into the clotting blood. This latter defect was usually secondary to some other disturbance, such as uraemia. The association of abnormal platelet function with altered morphology as defined by electron microscopy was illustrated by Dr. J. W. REBUCK, of Detroit, and Dr. H. BRAUNSTEINER, of Vienna. The latter claimed the discovery of a familial platelet defect characterized by abnormal morphology and the inability of the platelets to undergo metamorphosis, but with normal clot retraction.

Thrombopoiesis: Thrombokinetics

The kinetics and biodynamics of thrombopoiesis were described by Dr. E. P. CRONKITE, of New York, Dr. R. KINOSITA, of California, and Dr. C. A. FINCH, of Seattle. Drs. CRONKITE and KINOSITA produced evidence by the use of isotopes and tissue-culture to show that platelets are produced by megakaryocytes and that this latter cell is not self-perpetuating but can only mature to form platelets. Dr. FINCH showed that thrombocytopenia induced by thrombophoresis stimulates the marrow to increased production of platelets and suggested that the stimulating factor is a specific thrombocytopoietin which is contained in fresh normal plasma and in increased amounts in polycythaemic plasma. Certain types of thrombocytopenia might be due to a deficiency of this factor.

Thrombocytopenia

The concept of immune mechanisms in the production of thrombocytopenia was reviewed by Dr. W. J. HARRINGTON, of St. Louis, and Dr. J. L. TULLIS, of Boston. Dr. P. A. MIESCHER, of New York, described how he had demonstrated the adherence of soluble antigen-antibody complexes to the surface of platelets by means of fluorescent-antibody techniques. Dr. C. C. SPRAGUE, of New Orleans, detailed similar techniques used in an attempt to define anti-platelet factors in the blood of thrombocytopenic patients.

(Continued from next column)

renal disease. It is best avoided when the patient has liver damage unless very frequent estimations of serum glutamic oxalacetic transaminase can be done. It should not be given in pregnancy. Abortion has occurred during treatment in the first three months of pregnancy, and there is still insufficient knowledge about the effects of the drug upon the foetus.

Side-effects.—These are related to the size of the dosage employed, and include: postural hypotension (more severe in older patients), dizziness, paraesthesiae, muscle twitching, dyspnoea, oedema, headache, blurred vision, dryness of mouth, delayed micturition, impotence, constipation, feeling of weakness, sweating, insomnia, dermatitis, acne-like spots over upper half of body, and anaemia. No cases of jaundice have been reported, and serial estimations of serum transaminase have been uneventful. Nevertheless, the possibility of liver damage should always be borne in mind and the drug stopped immediately should jaundice occur. Oedema can usually be controlled by chlorothiazide. Anaemia, which resembles that of iron deficiency, responds to pyridoxine and iron. Headaches may be intense, throbbing, and felt over the back of the head and neck, and are an indication that the dosage should be reduced. Marplan potentiates the effects of drugs such as barbiturates, phenothiazines, and alcohol. All patients given the drug should be warned of this, especially about alcohol, and of the possible risks of driving after taking a "normal" amount of alcohol.

N.H.S. Basic Price.—100 10-mg. tabs., 15s. 10d.

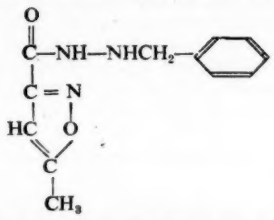
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Isocarboxazid

"Marplan" (Roche).

Chemistry.—This is 3-benzylhydrazinocarbonyl-5-methylisoxazole:



Pharmacology.—Marplan is an amine oxidase inhibitor and is thought to act by affecting the metabolism of 5-hydroxytryptamine and catechol amines such as noradrenaline. However, there is lack of correlation between the degree of monoamine oxidase inhibition and clinical effectiveness of this group of drugs, and it now seems likely that other actions, such as inhibition of decarboxylase activity, may be concerned.

Therapy.—Much research has recently been done in trying to produce a drug as clinically effective as iproniazid but lacking its toxicity. None of the newer drugs is as effective as iproniazid, but marplan seems to be one of the best of these. Patients with neurotic, or reactive, types of depression, in the setting of a good previous personality, generally respond well. Patients with endogenous depression are less responsive, probably because of the greater depth of the depression, and where there is accompanying agitation E.C.T. should not be delayed. Marplan can be given at the same time; there is some evidence that fewer electroshocks are then needed, and subsequent relapses prevented. Recurrent depressive illnesses may sometimes be stopped, or considerably lightened, by a small maintenance dose of marplan, increased when an attack is due or felt to be starting. Marplan should never be given in acute schizophrenia, as symptoms may become much worse. But many schizophrenics, once symptoms are controlled by a phenothiazine, subsequently become depressed. Provided there is no anxiety present and the phenothiazine is continued, marplan is often very effective in abolishing such depression. Marplan, like iproniazid, is also useful in the symptomatic relief of angina pectoris.

Dosage.—10 mg. (1 tablet) three times a day is the starting dose. Response varies in time from a few days to a fortnight, and the maximum response often takes four weeks. If no improvement has occurred at the end of a fortnight the dose should be increased to 20 mg. twice a day for a further week. It is usually pointless to continue if there is no improvement at the end of this time. Once symptoms are controlled, marplan needs to be continued until the underlying illness terminates itself. The dosage can usually be reduced to between 10 and 30 mg. a day.

Contraindications are similar to those for other monoamine oxidase inhibitors. Marplan should not be given alone in severe endogenous depression, or where there is much coexistent agitation, as suicide may become a serious risk. It may also cause anxiety to flare up in tension states, and, when the underlying personality is also unstable, disorders of behaviour may occur. For this reason marplan should not be given to psychopathic persons unless there is close supervision. Rarely, and usually only with large doses, hypomanic states may occur in the course of treatment. Marplan should be used with caution in cases of

(Continued at foot of previous column)

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Oral Diuretics in Pregnancy Toxaemia

SIR,—We would like to draw your attention to what we consider to be a misuse of a most valuable new series of drugs. We have now seen five cases of intrauterine death following the use of diuretics of the chlorothiazide type in toxaemia of pregnancy.

The first two cases occurred in our own department after we ourselves had prescribed moderate doses of this drug. The oedema lessened, the blood pressure became lower, and the foetus died. We have now seen three cases referred to us from general practitioners outside, with the same sequence of events.

We believe that two valuable signs of toxaemia of pregnancy are minimized or lost, while the toxaemic process continues. The warning to rest the patient more completely or to induce labour being absent, the correct measures for the control of the toxaemia are delayed. We have not yet seen any dire effect on the mother following the use of oral diuretics, but the loss of five babies in three months makes us consider that further research into the action of oral diuretics in the toxaemia of pregnancy should be carried out before manufacturers claim that it is a useful drug in this serious condition.—We are, etc.,

JOHN D. WATT.
ELLIOT E. PHILIPP.

Oldchurch Hospital,
Romford.

Familial Intestinal Polyposis

SIR,—I was very interested to read the leading article on familial intestinal polyposis (May 28, p. 1627). It is a most useful summary of the present position of these diseases. I do, however, disagree with the opening sentence, which states that adenomatous polyps are not uncommon in childhood. Superficially this is true, but the article does not point out that there is a definite clinical, and I believe pathological, entity, the congenital polyp. This is quite unlike the adenoma seen in the adult rectum and colon at sigmoidoscopy, which has the same appearance as that seen in familial polyposis coli and has the same predilection for malignant change.

The congenital polyp is compact and not lobulated, it is a much brighter red (not plum-coloured), and shines on account of adherent mucus. It is more commonly single, though it may be multiple, and it is usually on a short pedicle. It does not undergo malignant change. Congenital polyps commonly cause bleeding in early childhood, but it is uncommon to see them in the adolescent. They tend to fall off, and it seems probable that many are never found for this reason: the more profuse bleeding which takes the child to the doctor has occurred as the polyp has been shed.—I am, etc.,

London, W.1. IAN P. TODD.

SIR,—In your otherwise excellent leading article on familial intestinal polyposis (May 28, p. 1627) you state in your opening paragraph that adenomatous polyps of the large intestine are not uncommon in childhood and that the polyp is usually single. I do not think this statement should be made without some reference to the so-called congenital polyp of the rectum and colon, which is not uncommon in childhood, and is often confused with true adenomatous proliferation. Moreover, I would suggest that true adenomata of the large intestine other than those seen in familial polyposis are very rare in children.

The congenital polyp is usually single. It may be multiple and is a cause of bleeding from the rectum in both children and adults. It is round, with a smooth surface, whereas the adenoma is a lobulated tumour in its developed state. The cut surface appears cystic, and under the microscope is composed of rectal tubules lined by well-differentiated mucus-secreting epithelium lying in a stroma of connective tissue resembling primitive mesenchyme. The tubules tend to become dilated with excess mucus secretion, which explains the cystic appearance on inspection of the cut surface. The amount of stroma in proportion to the epithelial element is much greater than in an adenoma. The congenital polyp of children and young adults is probably a malformation, a hamartoma rather than a true neoplasm, and should not therefore be regarded as precancerous. These polyps are not directly related, as far as we are aware, to any of the forms of familial intestinal polyposis mentioned in your article.

There is also considerable histological evidence that the polyps in the Peutz–Jeghers syndrome are malformations or hamartomas rather than true neoplasms, which would account for the very low risk of carcinoma in patients with this disease. The polyps are composed of well-differentiated epithelium covering a stroma composed of smooth muscle, which probably represents a malformation of the muscularis mucosae. The appearances are quite unlike those seen in adenomatous proliferation. Personally I do not think there is yet sufficient evidence for regarding Peutz–Jeghers polyps as a precancerous lesion. Apart from the risk of malignancy being very low, the histological transition from an obviously benign appearance through the changes of "carcinoma *in situ*" to frank invasion of adjacent tissues has not been demonstrated.—I am, etc.,

Pathology Department,
St. Mark's Hospital,
London, E.C.1. BASIL MORSON.

Intestinal Fat-absorption

SIR,—We read with interest the article by Mr. W. F. Walker, Dr. W. K. Stewart, Dr. H. G. Morgan, and Mr. J. McKie (May 7, p. 1403) on intestinal fat-absorption, in which they suggest a rapid screening-test based on the urinary excretion of ^{131}I in the first 24 hours after ingestion of radioactive fat. For nearly four years, this department has routinely employed the radioactive fat-absorption test as described by Lubran and Pearson[1] and Veall and Vetter,[2] which depends on faecal collections. In our preliminary studies on patients and controls both faecal and urinary collections were made. The results are shown in the Table and it will be seen that one patient with marked malabsorption of fat excreted a small percentage (10%) of radioactive ^{131}I in the urine in the first 24 hours, two patients with normal absorption excreted less than 30% of the radioactive ^{131}I in the urine in the first 24 hours, and two patients with equivocal results (6.7 and 7.8% in the faeces) and one with a normal faecal excretion excreted less than 50% in the urine in the first 24 hours. Another patient with an equivocal result (6% in the faeces) excreted 65% in the urine. In view of these results the

An Analysis of the Excretion of Radioactive ^{131}I in 13 Patients and 5 Controls Following a Dose of 5 μC of Radioactive Iodinated Triolein

Cases	Per cent. Radioactivity in 1st 24-hr. Urine	Per cent. Radioactivity in Faeces (5 Days)
0	0–9	—
1	10–19	30
2	20–29	1 3·2*
0	30–39	—
3	40–49	4·9 6·7 7·8
1	50–59	3·4
4	60–69	1·0 3·4 4·0 6·0
5	70–79	2·0 2·4 2·9 3·0 3·6
2	80–89	0·1 3·4

* This patient excreted in the urine 23% in the first 24 hours, 17·6% in the second 24 hours, and 20·2% in the third 24 hours.

urinary excretion was not further considered as a possible diagnostic test.

We feel that the more laborious faecal collections have certain theoretical advantages over the suggested technique of a 24-hour urine collection. Firstly, the faecal estimation is based on the simple assumption that the unabsorbed labelled fat is directly measurable, whereas the method based on urine depends partly on other variables, such as an unknown proportion of the ingested fat which may be laid down in the fat depots or even an incompletely blocked thyroid gland. Since urine measurements are an indirect means of ascertaining the average level of inorganic radio-iodine present in the plasma during the period of collection, the values obtained will depend on the rate at which the radioactive iodine is split off from the fat by metabolic processes. Secondly, faecal collection avoids the need for having to pay regard to renal function. Thirdly, as pointed out by Lubran and Pearson,[1] by having the patient on a known fat-intake a chemical fat balance may be performed if equivocal results are obtained without the delay entailed by a further collection of specimens.

On the other hand, the suggested dose of 1 μC for the urine method is lower than the 5 μC used by us in adult cases. Furthermore, although faecal and urine admixture would invalidate both methods, faecal contamination of urine is recognized more easily. As collection of a 24-hour urine is simpler and quicker than a 5-day faecal collection, the further experience of Mr. Walker and his colleagues with their test will be awaited with interest, especially in respect of patients in whom there is only slight or moderate fat malabsorption when the diagnostic value of the fat-absorption test is at its greatest.—We are, etc.,

P. D. GRIFFITHS.
R. G. HUNTSMAN.
A. R. H. WORSSAM.

Department of Clinical Pathology,
Guy's Hospital,
London, S.E.1.

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2 Veall, N., and Vetter, H., *Radioisotope Techniques in Clinical Research and Diagnosis*, 1958. Butterworth.

Sleep and Rhythmic Stimulation

SIR,—I should like to make two comments on Dr. Ian Oswald's paper (May 14, p. 1450) on falling asleep during intense rhythmic stimulation. The first is that Dr. Oswald has been using a hypnotic process for inducing sleep, although he has not said so explicitly. Kubie and Margolin[1] in their paper on the process of hypnotism have shown that to produce the desired state requires certain conditions—namely, a state of relative immobilization with the field of attention focused on one area, causing withdrawal of attention from others. Other conditions required are the production of a state of monotony dependent on adaptation to the sensory stimuli. This is enhanced if the stimuli are rhythmic. Dr. Oswald's procedure meets these requirements and it is not surprising that these subjects should pass into a hypnotic state. If this conclusion is valid then the reason for the type of sleep produced by Dr. Oswald—that is abrupt, transitory, and in the presence of intense sensory stimuli—is apparent. Oswald has produced a hypnotic state which passes into hypnotic sleep. I would draw his attention to the paper by Barker and Burgwin,[2] where they showed by means of the E.E.G. that these two states are distinct entities.

My second comment arises out of Dr. Oswald's interesting observation that intensive rhythmic stimulation will produce sleep especially if the eyes are closed, and that in some cases repetitive movements will continue in sleep. This observation of his could explain the puzzling behaviour of infants who rock themselves to sleep and may continue to rock in their sleep in a violent manner. In the line of Dr. Oswald's findings this behaviour can now be explained as an attempt on the part of the infant to produce sleep as a result of auto-hypnosis, or, as Dr. Oswald would prefer to say, by transmarginal inhibition.—I am, etc.,

London, S.E.5. JOHN EVANS.

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Disinfection of the Hands

SIR,—We were most interested in the recent paper "Disinfection of the Hands of Surgeons and Nurses," by Dr. E. J. L. Lowbury and Mr. H. A. Lilly (May 14, p. 1445), and in the work of Dr. H. G. Smylie and his colleagues (October 3, 1959, p. 606) that showed the promising results obtained by the use of hexachlorophane in operating-theatre scrubbing techniques. We also have performed experiments during the past five months in the operating theatres of the Middlesex Hospital to test both pre- and post-operatively the efficiency of various antiseptics, amongst which were those used by the other workers. We used six surgeons working under normal operating conditions for all our observations.

Firstly a control scrubbing technique was used by the six surgeons for fourteen days. This consisted of five minutes' scrubbing with bar soap followed by a 95% alcohol rinse. After every scrub impressions from the dorsal and volar surfaces of each surgeon's hands were taken on to blood-agar plates prior to putting on gloves, and a similar procedure was carried out post-operatively after removal of the gloves. The plates were then incubated at 37° C. for 24 hours and the number of bacterial colonies per finger impression counted. The duration of each operation was also recorded in minutes.

Following this fourteen-day control period, four different antiseptics were tested in turn: (1) "phisohex" cream (containing 3% hexachlorophane), (2) soap containing 2% hexachlorophane, (3) "dettol" antiseptic cream, (4) "hibitane" (chlorhexidine diacetate) obstetric cream. The same technique was used for (2), (3), and (4) with the omission of the 95% alcohol rinse, and in the case of (3) and (4) the substitution of dettol antiseptic cream or hibitane obstetric cream.

In the case of the phisohex trial, the following four-minute scrubbing method was used: (1) 2 ml. phisohex was

taken into the palm of the hand and sufficient water added to produce a lather and rubbed into the hands and arms to just above the elbow for one minute. (2) Rinse in running water. (3) Clean nails with a brush and phisohex under running water. (4) Repeat stage one for two minutes, covering the skin area as far as the elbow. (5) Rinse in running water. (6) Dry on sterile towel.

The bacterial counts recorded for each antiseptic are summarized in the Table.

Summary of Bacterial Counts

	Pre-operative		Post-operative	
	Volar	Dorsum	Volar	Dorsum
5 min. scrub+95% alcohol	77	128	105	132
Phisohex	33	41	8	6
2% hexachlorophane soap ..	90	131	102	101
Dettol antiseptic cream ..	137	150	150	137
Hibitane obstetric cream ..	81	114	125	125

These figures represent the average bacterial counts for all six surgeons over the whole two-week test period of each antiseptic tested and the control scrub.

It may be seen from the Table that under theatre conditions our results are essentially similar to those of Dr. Lowbury and Mr. Lilly. It was also noted that in the case of phisohex there was a definite time relationship between the duration of the operation and the bacterial count. We estimated that under theatre conditions the maximum activity of phisohex was attained between 30 and 40 minutes after application and that the activity was maintained for at least four hours. This effect was not observed with any of the other antiseptics used.—We are, etc.,

R. E. M. THOMPSON.
J. O. W. BEILBY.

Bland-Sutton Institute of Pathology, Middlesex Hospital, London, W.1.

SIR,—I read the article on "Disinfection of the Hands of Surgeons and Nurses," by Dr. E. J. L. Lowbury and Mr. H. A. Lilly (May 14, p. 1445), and your leading article on the same subject (p. 1489) with great pleasure. I have been advocating gloves for nurses for some years now, with very little success. I described the experiments which led me to take this view in a letter to the *Lancet* (September 13, 1958, p. 588) rather briefly.

The effectiveness of 70% spirit was shown some years ago by experiments by Story.[1] The skin of the fingers is really a fairly thick sponge. Washing the hands removes superficial dirt and some organisms; then soaking the hands for 60 seconds in strong spirit (absolute commercial methylated spirit) enables the depths of the finger-tip sponge to be reached. If a non-irritating antiseptic is added to this spirit, all the better: very weak tincture of iodine is effective—so weak that, when added to the spirit in which the fingers are to be dipped, the colour of the solution is pale dry sherry. Other antiseptics such as weak chlorhexidine or hexachlorophane are probably equally effective (as Dr. Lowbury and Mr. Lilly have shown) and less irritating to the skin. The point that I would like to bring out is that strong spirit alone is effective, and only spirit will reach the depths of the skin sponge. A harmless antiseptic that will be adsorbed to the epithelial cells of the skin and can be dissolved in the spirit will maintain sterility in the gloved hands, even when sweating.—I am, etc.,

St. Margaret's Hospital, Epping. FRANK MARSH.

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[1] Story, P., *Brit. med. J.*, 1952, *2*, 1128.

Radiological Health and Safety

SIR,—In your annotation on radiological health and safety (May 14, p. 1492) the Veale Committee is reported as recommending that "the basic medical curriculum might include enough instruction in the use and hazards of ionizing radiation to give a clear picture of the scientific principles involved and the significance of the effects."

This statement is a reflection on the way in which undergraduate medical training in this country fails to provide adequate instruction in the medical uses of ionizing radiations. By no means all of the teaching hospitals give even elementary out-patient instruction in the uses of radiotherapy, and the result of this neglect is that house-officers undertake responsibility on the wards and possibly later in general practice in ignorance of the main indications and effects of a principal anti-cancer agent.

Apart from the uses of ionizing radiation in treatment, the practitioner may now be expected to be conversant with its effects on the developing embryo and the risks of cancerogenesis incurred by his patients who undergo diagnostic *x*-ray procedures. Whilst a short series of lectures could supply the basic knowledge of radiobiology, the need for a more enlightened approach to the part of radiotherapy in the treatment of cancer can only be met by clinical out-patient or ward teaching.—I am, etc.,

Hull, E. Yorks. J. S. BUNTING.

Survival in Nuclear War

SIR,—I share the concern of Mr. K. W. Monsarrat (March 12, p. 804) and Dr. N. T. Pollitt (May 7, p. 1434) that this country should lead the way out of the present nuclear deadlock; and in particular that a profession with a scientific and humanitarian basis such as ours should help to lead opinion in the direction of a sane and humane policy.

This country is at present spending astronomical sums on a form of defence which, on the Government's own admission, cannot defend us; the most it can hope for is to defend the bases from which retaliatory attacks would be launched in the event of a nuclear attack upon us. But when we are informed by military and scientific experts that a full-scale nuclear attack upon Russia would also kill 10 million people, either in India or in Western Europe, depending upon the prevailing wind—and that the biological and genetic effects are unpredictable but certainly evil—should we not as a profession give the strongest possible lead to public opinion by demanding that this nation should renounce the use of nuclear weapons? To those who still feel that the only alternative to retaining the "nuclear deterrent" would be enslavement to an abhorrent totalitarian regime, I would recommend *Defence in the Nuclear Age* by Sir Stephen King-Hall (Gollancz); and to all doctors concerned about the medical effects of nuclear warfare, *Hiroshima Diary*, written by a Japanese physician, Dr. M. Hachiya (Gollancz).—I am, etc.,

Liverpool, 23. ARTHUR SPEIGHT.

Strontium-90 in Human Bone

SIR,—Your leading article on the levels of strontium-90 in human bone (April 9, p. 1117) seems to end on a note of rather undue complacency. In view of the fact that this issue has become one of universal importance, one naturally appreciates any attempts to clarify the

significance of statements which previously, in your own words, have been "widely misquoted and misunderstood."

It may well be that, as you say, the statement of the Medical Research Council[1] was unduly pessimistic, but hardly on the basis which you suggest. There is an important distinction between reaching these critical levels "unexpectedly" (a word not used in the report, because, I suspect, it is quite irrelevant) and reaching them inevitably. While few would quibble that the former is exceedingly unlikely, there is considerable reason to wonder whether an equally complacent attitude can be maintained about such levels being attained in due course if testing is continued. Perhaps in view of the recent French explosions it would have been more accurate to have pointed out that the levels of strontium-90 would reflect the resumption of testing after an interval of a year or so.

Finally, in all fairness, it would seem fitting for you to emphasize that the so-called "maximum permissible occupational level" has by no means been irrevocably established. Hempleman's recent review of the subject,[2] would suggest that the maximum might very well be considerably less than the figures you have quoted.—I am, etc.,

London, W.2. I. B. PLESS.

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Mongols with Leukaemia

SIR,—The occurrence of an abnormal chromosome constitution in mongols may have significance other than simply in relation to the aetiology of mongolism.[1-4] The possible role of the extra chromosome material in determining the increased risk of mortality from leukaemia which has been found in mongols[5-7] may well be relevant to the general problem of leukaemogenesis. Such relevance seems the more likely in view of the demonstration of chromosome abnormalities in some cases of acute leukaemia.[8 9] We have been trying for over a year to study the chromosome constitution of mongols with leukaemia. Such cases are, of course, fairly rare, but during this period we have had the opportunity of studying two such patients. However, during the same period we heard of a further four cases only after death, and the clinicians concerned expressed regret that they did not know of our interest.

It is for this reason that we seek wider publicity for our wish to study mongols with leukaemia. Although the blood and bone-marrow samples for chromosome studies require special handling immediately they are obtained, it must be emphasized that such samples can be taken at the same time and in the same way as those required for ordinary diagnostic purposes. We would be grateful for the opportunity to study these patients anywhere in Britain.—We are, etc.,

A. G. BAIKIE.
W. M. COURT BROWN.
P. A. JACOBS.

M.R.C. Group for Research on the General Effects of Radiation, Western General Hospital, Edinburgh, 4.

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Intelligence and Prematurity

SIR,—I should like to comment briefly on Dr. C. M. Drillien's letter in your issue of April 30 (p. 1361). It is not correct to say that in my studies of the mental development of premature children[1-3] "radically different conclusions have been drawn from the three age-groups studied." My single conclusion is that this group of premature children appear to show an increasing mental handicap as they grow older, but that this is more likely to be a result of the poor home environment in which they grew up than of prematurity *per se*. The results of mental and scholastic tests at both 8 and 11 years and of the 11+ selection examination support this hypothesis and the fact that these children were not retarded in walking or talking (after allowance is made for the degree of prematurity) does not contradict it.

I am glad that Dr. Drillien has underlined some of the points I made on the difficulties of choosing controls, but she seems to miss the point that many of the factors that turned out to be important for educational progress—for example, the lack of interest taken in the premature children's progress at school—could not have been measured at the beginning of the inquiry, and this holds also for social factors such as subsequent unemployment. This underlines the need for continuing study of these families. Dr. Drillien is incorrect when she implies that I have been "going back over eleven years [to] unearth data." The data used were collected during the ordinary course of this study and have been used as they became available. Dr. Drillien should be aware of this, as we have often discussed the results of our respective studies here in Edinburgh.

Dr. Drillien quotes her own survey[4] as having the advantage of a randomly selected group of controls rather than matched controls, and cites my paper and your annotation (April 2, p. 1036) in support of this. But surely the point made in the annotation was that it was desirable to deal with this type of problem on the basis of following up a large proportion of the population of births rather than just a few. In Dr. Drillien's survey the "control" group consists of 119 singletons with birth weights of over 5½ lb. (2.48 kg.), who are used as the controls to 251 singletons weighing 5½ lb. or less. With these small numbers it is impossible to make allowances for the complex web of biological and social factors associated with prematurity and with the later development of premature children. With a randomly selected control group twenty times the size it might be possible.

I do not wish to enter into an argument as to the relative value of large and small surveys. The National Survey, however, has the great advantage that all assessments, whether by teacher or school doctor, were done by persons who did not know the birth-weight of the child. This removed a potentially serious source of bias. One last point; having been taken to task by Dr. Drillien in the past for *not* using the "Registrar-General's classification of father,"[5] it is hard that she should now accuse me of using it.—I am, etc.,

Department of Public Health and Social Medicine, University of Edinburgh. J. W. B. DOUGLAS.

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"Cancer of the Skin"

SIR,—Dr. F. Ray Bettley's review (March 5, p. 708) of Dr. John C. Belisario's book, *Cancer of the Skin*, was most unfortunate. It is amazing that this book, which has had favourable reviews from so many quarters and is so highly regarded in this country, should receive hardly a word of commendation from Dr. Bettley. It is more surprising still that the reviewer obviously knows so little about skin malignancy and nothing about Australian conditions. One who, on his own admission, does not treat cancer of the skin is obviously not qualified to comment on a book such as this.

Dr. Belisario's book should be strongly recommended to all interested in this subject. It is highly regarded by Australian dermatologists, all of whom see and treat large numbers of cases of cancer of the skin.—We are, etc.,

L. W. LINN.
Adelaide, South Australia. HOWARD W. LINN.

SIR,—I have just read Dr. F. Ray Bettley's review (March 5, p. 708) of the book *Cancer of the Skin*, by Dr. John C. Belisario. I find it very difficult to understand why he should have written in the way he did, to endeavour to give the impression that the book was of mediocre or poor quality. He could not have read it very throughly in at least some of the parts he criticized, or he would not have imputed to Dr. Belisario statements of other people (e.g., Cipollaro (1947) on p. 15 and Lehman on page 26) which Dr. Belisario was quoting.

Also a large number of reviews have now appeared in medical journals from all over the world, and every one of them has been highly complimentary about the book, and many full of the highest praise. In view of this it would appear to be a little unfortunate that Dr. Belisario's book should have been given for review to someone who is obviously out of step with world opinion on the subject of skin cancer.—I am, etc.,

Sydney, Australia. M. T. HAVYATT.

SIR,—I was astonished, to say the least, when I read Dr. F. Ray Bettley's review (March 5, p. 708) of Dr. John C. Belisario's recent book *Cancer of the Skin*. As a dermatologist who has practised for more than 30 years in Queensland, and in that time has seen, and treated, many cases of skin cancer and precancerous conditions, I can say with confidence that Dr. Belisario's book is the most informative work on skin cancers that has ever been published.

For the reviewer to throw doubt on the statement that skin cancer occurs more frequently in those people of a fair skin and blue eyes, whose origin or whose forebears were in a land where there was very little sunlight, shows a considerable lack of knowledge of the subject. In the past, Herman Lawrence in Melbourne, Molesworth, Johnson, and Paul in Sydney, to mention only some of the dermatologists of Australia, all have drawn attention to this fact, and it has been clearly established that such is the case. Similar conditions would apply in the United States, and we would expect to find a higher incidence of skin cancer in the States, near the Tropics, and again in people whose origin was in a country with very little sunshine.

His remarks on the occurrence of skin cancer in lupus erythematosus and lupus vulgaris seem to be beside the point. We see many cases of lupus erythematosus in Australia, and at times we see skin cancers occurring in the lesions, whereas lupus vulgaris is extremely rare—this is so well known that one would expect a British dermatologist to be aware of this fact.

Radiotherapy and other forms of treatment of primary skin cancers and precancerous conditions are *always* (not often) undertaken by dermatologists in Australia, and, I can assure Dr. Bettley, with excellent results, both from a curative and a cosmetic point of view.

Dr. Belisario to-day ranks as one of the great authorities on skin cancer in the world. He has put together in the book his many and varied experiences, and he has shared all these experiences, at all times, with his colleagues. He has covered every aspect of this subject, and he has illustrated his work with the very best reproductions that were available—it is not always easy to secure good photographs of rare conditions, but he has managed to produce and reproduce a remarkable collection to illustrate his book. For that, and many other reasons, we are justly proud of his work. I feel that your reviewer has done a real injustice, in the wording of his review, to a very valuable contribution to medicine generally.—I am, etc.,

Brisbane, Australia. B. B. BARRACK.

SIR,—In case anyone is tempted to take it as expressing general dermatological opinion, I should like to comment on Dr. F. R. Bettley's review (March 5, p. 708) of Dr. J. C. Belisario's book on skin cancer. I feel that Dr. Bettley, with his mixture of minor criticisms and sublaudatory damnation, does less than justice to an important work by the leading expert of a country with the world's highest incidence of this disease. For instance: Dr. Bettley takes Dr. Belisario to task over some statistics he quotes in the words: "Most dermatologists in *Europe* would consider . . ." (My italics.) If you take the trouble to look up the passage in question you find that it refers to figures from a paper in the *Texas State Journal of Medicine*.

Another surprising statement is, "The radiotherapy of primary carcinoma of the skin, particularly of smaller lesions, is often undertaken by dermatologists in Australia *even as an office procedure*." (Again my italics.) Although in this country we do not see as much skin cancer as they do in Australia, it is commoner here than in Great Britain and we have yet to see one of these lesions treated by radiotherapy other than as an "office procedure." If English dermatologists, as Dr. Bettley says, really do hand this important part of their work over to radiotherapists, that is a matter to be hushed up decently rather than shouted from the housetops.—I am, etc.,

Wellington, New Zealand. R. G. PARK.

*** We showed the above four letters to Dr. Bettley, who replies as follows.—ED., *B.M.J.*

SIR,—First, I must apologize to Drs. L. W. and Howard Linn for not making myself quite clear. My comment regarding the treatment of carcinoma was that in the United Kingdom most dermatologists ask the radiologist to carry out radiotherapy. I did not intend to convey the impression that radiotherapy is the only treatment used in this country. Indeed, the majority of my cases are not dealt with in this way. If, therefore, I gave the impression that I do not treat cancer of the skin, this is quite misleading.

I wonder whether Dr. M. T. Havyatt has read Dr. Belisario's book and my review quite as carefully as he would suggest. The reference he gives on page 15 quotes figures

given by Cipollaro, but the interpretation of these figures is Dr. Belisario's. I believe that this is perfectly clear from the grammatical construction. In regard to the reference on page 26, I now find that in fact Dr. Belisario misquoted Lehman. In the reference given Lehman says "in lupus vulgaris, 0.5–4%." Belisario quotes "in lupus vulgaris 0.5%." It was this low figure that particularly prompted my comment, and had Dr. Belisario quoted Lehman correctly my comment would not have been called for. In fact, Lehman is himself quoting Montgomery, and in Montgomery's article it is clear that the figures for lupus vulgaris originate from a different source than those of lupus erythematosus. The series are therefore not strictly comparable, and Montgomery wisely refrains from drawing this comparison. In these circumstances I cannot understand why Dr. Havyatt should think that Dr. Belisario is not responsible for what appears in his book.

Regarding skin colour and sunlight, Dr. B. B. Barrack misinterprets my remarks. I certainly did not question that skin cancer occurs more often in fair subjects, for of this I think there can no doubt. My comment was that Dr. Belisario states the conclusions and supports them with evidence which is not valid. My criticism was of Dr. Belisario's evidence and not of his conclusions. Dr. Barrack says that lupus erythematosus is more common and lupus vulgaris is rare in Australia; the same is true in the United Kingdom, but this is not the point under discussion and bears no relation to the percentage incidence of carcinoma in the two conditions.

I should not like Dr. Barrack to think that I criticize Australian dermatologists for their radiotherapy. My comment was that radiotherapy is usually carried out by radiologists in the United Kingdom and I did not suggest that either system was preferable. Finally, Dr. Barrack mentions illustrations, and I would remind him that I described some of these as very good. It is quite understandable that some will be below standard. It would be invidious to pick these out, but I think anyone may verify that some are below standard and that the colour plates are of variable quality.—I am, etc.,

London, W.1. F. RAY BETTLEY.

Undescended Testicle

SIR,—May I answer various points which have been put to me? The distinction between the inguinal ectopic and the high retractile testicle, which Mr. J. A. Rhind (May 21, p. 1567) rightly sees as the crux of diagnosis, is that in the former the testis on being coaxed downwards goes into the fold between the thigh and the scrotum, whereas the latter type can be worked over the bar of the pubic bone. I suggest it would be a good thing to stick to the carefully thought-out nomenclature of the paper which started all the trouble[1]; "high retractile" has a definite meaning, "incompletely descended" has not. As to giving him a formula which will enable him to foretell the date of the final assumption of the adult position by retractile testes, I wish I could; but the variables of patient, observer, and nomenclature make this impossible. It is far more difficult than foretelling when a boy will grow a proper beard; heredity and physical type are important factors.

All Mr. K. M. Backhouse's letters (see May 14, p. 1508) have puzzled me, as he shows no understanding of the teaching he attacks. He says he confutes me by getting testes into the "canal" at operation, but he does not say what the operation was. The argument is about normal inguinal canals, and, as operations on them are far from common, I would like some more information. I do not know if it has occurred to him that he also has a feud with classical anatomy; since if he is right all textbook pictures of the external ring will have to be redrawn to make it big enough to take the testis, plus the folded-up cord and the cremaster (contracted to a degree that no other muscle of the kind can approach). My "direct attack" on anatomists does not end here. I assert that the internal spermatic fascia as they describe it no more exists[2] than did the six arteries they alleged to supply the tonsils, before I made an attack in that field.[3]

For those who would like to study the retraction of the testis I recommend the technique I use when operating on an apparently unilateral inguinal hernia in a child. This is to expose both external rings through a short transverse incision. The main object is to avoid the nuisance of a hernia showing up on the other side after the obvious one has been cured, but there are the other advantages of leaving an ultimately invisible scar and making it impossible to operate on the wrong side. If the surgeon first carefully exposes the intact fascia of Scarpa, and then pushes the testicle up under it, he will demonstrate the superficial inguinal pouch. Then exposure of the normal external ring which is found in most of these explorations will show the impossibility of getting the testis into it.—I am, etc.,

London, W.1. DENIS BROWNE.

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[1] Browne, D., *Brit. med. J.*, 1938, **2**, 168.
[2] —— *Lancet*, 1933, **1**, 460.
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Students' Acceptance of Psychiatry

SIR,—The letter under the above heading, by Dr. Amy M. Pantin (May 7, p. 1432) has two mistakes in it. (1) "Modern physics has demonstrated that the behaviour of ultimate particles is not predictable: in order to make one measurement, it is necessary to abandon another." The writer has got muddled over Heisenberg's Principle. This states that in a pair of related measurements in a small system, such as the position-coordinate and the momentum of an electron, each measurement has an inherent uncertainty, and the product of the two uncertainties is numerically equal to Plank's constant "h." It is false to say that in order to make one measurement it is necessary to abandon another. (2) To argue from Heisenberg's Principle to a denial of determinism, or indeed to any particular philosophical view, is very rash indeed, even though some bishops and the great A. S. Eddington have done it. The sentence, "The evidence of the natural sciences, therefore, as far as it has gone, does not support determinism," is, I think, very much too confident if stated in this unqualified way. To prefix it with "some have argued that . . ." would, however, be satisfactory.

Heisenberg's Principle is mathematical, and many doctors dislike mathematics. May I try to show by an analogy the kind of thing the Principle means? You might find a witness in court 100% credible if he said he entered the bank between 10 a.m. and 3 p.m.; 95% credible if he said between 11 a.m. and noon; 2% credible if he said between 11.27 a.m. and 11.28 a.m.; 0.0000001% credible if he said between 11.27 and 32 seconds a.m. and 11.27 and 33 seconds a.m. The greater the accuracy claimed, the less you believe his statement. But this state of affairs has not much to tell us for or against free will.—I am, etc.,

Totnes, Devon. HUGH HECKSTALL-SMITH.

Late Lactation

SIR,—I was interested to read of the case of late lactation reported by Dr. Margaret and Mr. Anthony Barker (April 30, p. 1365). There are a number of references in the literature to "lactation" occurring in post-menopausal women brought about by suckling alone outside the influence of pregnancy. According to some authors, children have been fostered entirely by post-menopausal women and even by men, and thus there seems little doubt that true milk or something very like it is secreted in many of these cases. However, chemical analysis of breast secretions is not reported, probably because suckling by old women is rare except among primitive peoples and in countries where adequate laboratory facilities are not available.

In England the commonest cause of secretion is duct ectasia. The discharge may be unilateral or bilateral and of appreciable volume, and there may be no other physical signs of this disease. The secretions may resemble milk in colour and consistency, but chemically they differ considerably in that lactose is absent, protein is present in much larger quantities than in true milk, and often red cells and the products of blood are present. For these reasons the assumption that the secretion is milk must in all cases be supported by chemical analysis.

It would be interesting to know whether the secretion reported by Drs. M. and A. Barker conformed to true milk or an abnormal secretion, particularly as duct ectasia is prevalent in the age group of their patient.

A full account and classification of breast secretions is shortly to be published.—I am, etc.,

St. James's Hospital, Leeds. J. A. DOSSETT.

Pitfalls in Chemotherapy of Tuberculosis

SIR,—I read with interest the article by Drs. Graham Poole and Peter Stradling entitled "Chemotherapeutic Pitfalls in the Treatment of Tuberculosis" (January 16, p. 161). I must join issue, however, with their assumption that all regimes of treatment other than those recommended by the Medical Research Council are "faulty." I refer particularly to the dosage and administration of streptomycin.

In 1950 a report to the British Medical Research Council's Streptomycin in Tuberculosis Committee[1] recorded the results of a trial using various regimes of streptomycin. As a result of this trial it was recommended that "1 g. of streptomycin a day in a single injection, without intermission of treatment, is the most satisfactory way of giving the drug in pulmonary tuberculosis." The Medical Research Council adopted these recommendations, and since then most countries throughout the world have one by one followed suit, and other regimes of streptomycin, including intermittent therapy, were gradually discarded. In the original trial three regimes of streptomycin were compared with a 1 g. a day regime. Unfortunately they would appear, by present-day requirements, to be most inadequate—namely, (1) 0.5 g. streptomycin six-hourly in alternate weeks; (2) 0.5 g. streptomycin six-hourly in alternate months; and (3) 0.25 g. streptomycin six-hourly continuously. Not one of these regimes permitted bactericidal concentrations of streptomycin, and it was obvious that 1 g. a day would be superior to any of them in efficacy and in the prevention of development of drug resistance. In a letter that year[2] I pointed out the advantages of administering a higher dosage of streptomycin in a single injection every second day and warned against complacently accepting 1 g. a day as the best of "all" regimes. In reply[3] one of the members of the trials committee agreed that there were theoretical reasons for suggesting a dosage of, say, 3 g. of streptomycin every third day, but stated that, although such a trial had been advocated from time to time, it had not been undertaken "owing to pressure of other investigations."

Since 1948 I have been investigating various regimes of streptomycin in combination with other drugs in over 1,000 cases of pulmonary tuberculosis treated in Adelaide. In the prevention of drug-resistance and subsequent relapse over a five-year follow-up period, 2 g. of streptomycin in a single injection given three times a week has been superior to any other regime, including 1 g. streptomycin a day. I have attributed these good results to the greater potential bactericidal effect of a 2-g. dose. Toxicity has been only slightly increased, and 1 g. streptomycin a day was tried in the handful of cases who exhibited evidence of this.

It seems tragic that intermittent streptomycin therapy is sweepingly condemned on the most inadequate basis of a 1-g. dose given thrice or even only twice a week. 2 g. of streptomycin given on Mondays, Wednesdays, and Fridays does permit bactericidal and therefore effective concentrations of the drug, and, despite some statements to the contrary, toxicity is minimal on this intermittent dosage scheme. Another factor is that this intermittent therapy can be given more easily as part of domiciliary treatment. Streptomycin is now given every 24 hours, apparently because the sun rises and sets during this period of time. Surely it would be more rational to time its administration according to the life-cycle of the organisms that it intended to kill—in the case of the tubercle bacillus, every 36–72 hours. 2 g. in a single injection is more potentially bactericidal, and as a result should be more effective in preventing the emergence of drug resistance by "adaptation." Also, by killing as opposed to suppressing growth of tubercle bacilli, the likelihood of subsequent relapse occurring must be considerably lessened.

Streptomycin is still one of our two most valuable drugs in the armamentarium against tuberculosis, but I would like to urge all practising tuberculosis physicians to reconsider their basic thinking on the method of administration of this drug before its potential has been lost as a result of ineffectual use.—I am, etc.,

Adelaide, South Australia. R. MUNRO FORD.

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2 Ford, R. Munro, ibid., 1950, **2**, 369.
3 Crofton, J. W., ibid., 1950, **2**, 527.

Inoculation Technique

SIR,—An efficient valve to prevent reflux into the syringe is available. I have such a valve at the moment. It is the one described by Professor Dr. R. Gispen,[1] of the National Institute of Public Health of Utrecht. This valve is ingeniously simple, robust, small, and cheap. It fits on to the ordinary needle so as to form a mere extension of the butt, and the combination can be handled just like a needle alone. Careful experiments that are fully described in the article referred to appear to show conclusively that the valve is fully efficient for its purpose. Given a 2-ml. (or even a 5-ml.) syringe, twenty or more needle/valve combinations used in rotation, and a continuously boiling sterilizer, each needle/valve combination should be given at least 10 minutes' boiling, which is enough to inactivate Virus B.[2] Use a stout Spencer-Wells forceps, grasping the valve

for taking off, and the needle butt for taking out of the sterilizer and putting on.

The valves can be obtained from Rijks Institut voor de Volksgezondheid, Sterrenbos 1, Utrecht, Holland.

—I am, etc.,

Caversham, Reading. E. C. H. HUDDY.

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[1] Gispen, R., *Lancet*, 1952, **2**, 171.
[2] Expert Committee on Hepatitis. First Report. *Wld Hlth Org. techn. Rep.*, 1953, **62**, 22.

SIR,—Is there anything wrong, given good eyesight, with inserting a fine hypodermic needle down the capillary tube of lymph, thereby pushing the lymph out on to the skin? It is very simple.—I am, etc.,

London, W.2. STELLA MURRAY.

SIR,—When I blew calf-lymph vaccine on the T.V. programme about immunization I little knew what a hornets' nest I was stirring. The correspondence started by Professor Thomas Anderson (March 19, p. 882) has lasted over two months. As the accused, I would like to reply to some of the critics and to sum the position up.

Two quite separate problems are involved. Firstly, should the vaccine be blown from the tube with the mouth (as I did on the T.V. programme), or should some other means be used to eject it? Secondly, there is the risk of causing hepatitis if inadequately sterilized syringes are used. No one is suggesting that blowing calf-lymph vaccine exposes the patient to the risk of hepatitis—the risk here is of secondary infection of the vaccination lesion.

As far as syringe sterilization goes, I am in complete agreement with all the critics who say that a fresh syringe with a fresh needle should be used for every injection. On the T.V. programme I took a fresh syringe and needle from my (water) sterilizer.

The blowing of calf-lymph from the capillary tube or the use of a teat from a baby's bottle or a special nipple raises other questions. I do agree that blowing with the mouth is not the best method. The difficulty I used to experience whenever I used a nipple was the flow-back of the lymph into the nipple when the broken end of the tube was pushed into the hole in the nipple. This can easily be overcome (I have now discovered) by breaking off only one end of the tube before pushing it into the nipple. My error does seem to have served a useful purpose. If local authorities (or the Ministry of Health) can now be persuaded to supply dry sterile syringes to G.P.s for their immunization sessions (as the London County Council propose to supply for the sessions held in their own clinics), then all the sterilization doubts raised by Professor Anderson will be dispelled.

May I once more be permitted to retain the anonymity granted me by the B.B.C., and sign myself

A GENERAL PRACTITIONER.

Medical History of Ipswich

SIR,—The Ipswich Medical Library has decided to set up a historical section of records appertaining to the origin and growth of medicine in Ipswich and district, involving hospital practice, general practice, and public-health practice. The historical section hopes to include documents, books, photographs, and instruments. Any help your readers can give would be appreciated and should be sent to the Ipswich Medical Library, Anglesea Road Wing, Ipswich and East Suffolk Hospital, Ipswich.

—I am, etc.,

IRENE HEWETT,
Librarian,
Ipswich Medical Library.

Translating from Russian

SIR,—I was very interested to read Professor D. H. Smyth's review (May 21, p. 1561) of Jablonski and Levine's *Russian–English Medical Dictionary*. When he lists absentees in the first group (words of Slavonic origin), he omits to say that all these are in Carpovich's *Russian–English Biological and Medical Dictionary*. In practice, using these two dictionaries in combination with a sound general dictionary, like Smirnitsky's,[1] gives the best results. This tends to offset a further disadvantage of Jablonski and Levine's work, which is that many insects and other animals of medical importance do not figure in it.

With regard to abbreviations, a most useful selective list,[2] with over 15,000 entries, has been compiled by the reference department of the U.S. Library of Congress.—I am, etc.,

Editorial and Translation Unit, W.H.O. Regional Office for Europe, Copenhagen, Denmark. ANDREW SHERRINGTON.

REFERENCES

[1] Smirnitsky, A. I., *Russian–English Dictionary*, 3rd ed., 1958. State Publishing House of Foreign and National Dictionaries, Moscow.
[2] Rosenberg, A., *Russian Abbreviations, a Selective List*, 2nd ed., 1957. Reference Department, Library of Congress, Washington, D.C.

POINTS FROM LETTERS

Congenital Dislocation of the Hip

Mr. G. P. MITCHELL (Edinburgh) writes: I wish to correct certain figures quoted in my letter (April 9, p. 1132) supporting the plea for early diagnosis of congenital dislocation of the hip, and I apologize for my unintentional misrepresentation. The number of dislocated hips "missed" prior to an early diagnosis campaign included both cases diagnosed as dislocation during the period and cases born during that period who developed complete dislocation subsequently proved by arthrography. A more correct comparison is obtained by comparing the stage of displacement at diagnosis only of children born during the three years prior to and following an early diagnosis campaign. The cases in the final column of the Table were supervised during the post-natal period by health visitors instructed on the importance of early diagnosis. In the cases diagnosed as dislocation the displacement was accompanied by inversion of the limbus proved by arthrography. It is realized that the large number of "predislocated hips" recorded here probably includes many variations of the normal acetabular roof inclination.

Children Born during Years:	1953–55	1956–58
Dislocation	7	1
Subluxation	0	8
Predislocation	0	15
Total	7	24

Two-glass Test

Dr. P. R. TIMOTHY NAIDU (London, S.W.6) writes: An hour-glass-shaped apparatus with a float trapped in the lower chamber could be used in the two-specimen test. As urine is passed, so the float seals the lower chamber as it fills. The upper chamber would then, of course, be the No. 2 stream. Modification could be made for the three-specimen test.

Obituary

JOHN F. FULTON, O.B.E., M.D., D.Sc., D.Litt. LL.D., F.R.C.P.

Dr. John F. Fulton, the Sterling professor of the history of medicine and formerly Sterling professor of physiology at Yale University, died suddenly at his home in Hamden, Connecticut, on May 29, at the age of 60. Dr. Fulton was a pupil of Sherrington and Harvey Cushing, and had an international reputation as physiologist of the nervous system, medical historian, bibliographer, and bibliophile.

John Farquhar Fulton was born at St. Paul, Minnesota, on November 1, 1899, the son of John Farquhar and Edith Stanley (Wheaton) Fulton. He was of the same family as

Photograph of a portrait painted in 1957 by Sir Gerald Kelly.

Robert Fulton, the artist, inventor, and engineer, who was the pioneer of the steamboat. His father was a practising physician who helped to found the University of Minnesota, and was largely responsible for the establishment of the medical school there.

John Fulton was a lively and adventurous lad, and after leaving St. Paul High School at 16 he set out alone for the west coast, found work with a surveying team there, and enjoyed enormously the new experiences and friendships which came his way. In 1917 he enrolled as a student in the University of Minnesota, and there came under the influence of Wallace Notestein, then professor of English History at Minnesota, now emeritus professor at Yale. During his student years he also worked as a "stack-boy" in the St. Paul Public Library, and spent so much of his time reading Tolstoy and other great writers that when he attempted the entrance examination to Harvard he failed. But there his passion for books was first aroused and his disappointment was mitigated by enrolment in the Army, from which he entered Harvard (without examination) as a "veteran" and graduated B.S. *magna cum laude* in 1921, having already published his first scientific paper as an undergraduate in *Acta Zoologica* (1920). In the same year he was admitted to Magdalen College, Oxford, as a Rhodes scholar. Soon after his arrival he was officially seconded to Cambridge for a time so that he might help the one-time vice-chancellor and Master of Christ's College, Sir Arthur Shipley, in the preparation of his classic of elementary biology entitled *Life*, an association which is recorded by the dedication of the book to "J. F. F." From Shipley, himself a celebrated gastronome, Fulton first acquired the interest in gastronomy which was later to make his hospitality memorable to visiting scientists from many countries.

Despite this brief influential episode, he graduated B.A. with first-class honours in physiology in 1923 and was rewarded by his appointment as Christopher Welch scholar and university demonstrator in physiology with the privilege of working in Sherrington's laboratory. He had already published eight papers, including studies of neuromuscular transmission, and in the following two years he increased the total to 27, many of them in the *Journal of Physiology* and the *Procedings of the Royal Society*. The numerous ancient libraries in Oxford were also a source of inspiration to his growing spirit of "medical humanism." Osler had been dead for two years when Fulton arrived in Oxford, but Lady Osler kept his house at 13, Norham Gardens as "The Open Arms" for all students from overseas. There he spent many leisure hours helping Dr. W. Francis, Osler's nephew, and Mr. Reginald Hill, of the Bodleian Library, to compile the celebrated *Bibliotheca Osleriana*, the catalogue of Osler's own library of medical history, which is now at McGill University. After graduating D.Phil. in 1925, he returned to Harvard soaked in the Oslerian tradition, and there was awarded his M.D., again *magna cum laude*, in 1927. Already recognized as a brilliant young physiologist by his seniors in that field, he was drawn back to Oxford in 1928 to take up a fellowship at Magdalen College, but in 1930 he accepted the chair of physiology at Yale—a post which was named the Sterling professorship in 1931—and so began the most fruitful and important period of his career in neurophysiology.

Writing 25 years later, Hebbel E. Hoff recalled that Fulton made a point of calling his new home

> "the Laboratory (and not the Department) of Physiology, so distinguishing between an environment for inquiry and an academic framework of organization . . . an environment that yielded a maximum of stimulation and a minimum of direction, and much perspective . . . aimed primarily at the development of individuals and their personal philosophy of Physiology, rather than the Physiology of the Professor."

Always able to fire others with his own enthusiasm and never didactic, Fulton influenced but did not direct the many important studies made in the Laboratory in subsequent years by workers from many countries in neurophysiology, electrocardiology, endocrinology, and aviation physiology. Fulton's own rapidly growing bibliography during these years (it was eventually to total over 400 papers and some 20 books) records the success with which he maintained his many and varied interests. His work on the brain of the chimpanzee provided the experimental data and the inspiration which led Egas Moniz to carry out the first prefrontal lobotomy in man in 1936; his classic textbook, *Physiology of the Nervous System*, first published in 1938, is a model of what such a book should be, and reveals the same impeccable scholarship which characterizes his *Selected Readings in the History of Physiology* (1930), his *Bibliography of the Honourable Robert Boyle* (1932; 2nd ed. in press), or his *Bibliography of Aviation Medicine* (1942). The work done at Yale on the physiology of man at high altitudes was to prove of the greatest value to the British and American Air Forces during the second world war.

Meanwhile he had been keeping pace with his intimate friend and colleague Harvey Cushing as a book-collector of Oslerian status, and when Cushing died in 1939 he was largely responsible for making effective Cushing's wishes in the establishment of the Cushing Library at Yale as a centre

of research and study in the history of medicine. Around this nucleus a new university department was established, and in 1951 Fulton was appointed Sterling professor of the history of medicine. His own magnificent library, which included every classic work in physiology and neurology as well as unparalleled special collections such as those of Robert Boyle and Kenelm Digby, was added to Cushing's, as also was that of Dr. Arnold Klebs, close friend of both Cushing and Fulton, and a great collector of and authority on medical incunabula. The new department soon became as productive and influential as the laboratory of physiology had been under Fulton's guidance. Despite his failing health he maintained a vast correspondence all over the world, especially assisting and encouraging young scholars and new institutions at a critical stage in their development. One of his last great services to education was to arrange for the expansion of his department to include the history of science, with an additional chair in that subject, to which Dr. Derek Price, formerly of Cambridge, has recently been appointed.

Among other important offices which Fulton filled with distinction were those of trustee of the Institute of Advanced Study at Princeton (from 1942) and trustee of the Osler Library (from 1950). *The Journal of the History of Medicine*, which he edited from the department at Yale is one of the leading journals in the field and bears the impress of his taste and learning. His biography of Harvey Cushing (1946) matches Cushing's own biography of Osler, and the trio will certainly be completed by a similar volume on John Fulton.

The international importance of Fulton's work was recognized by no fewer than 26 decorations and honorary degrees awarded by governments and universities of many countries, but Britain was his second home, and those which he cherished above all were the Honorary O.B.E., conferred for his services to Britain during the war, the Oxford D.Litt., which he received in 1957, the Fellowship of the Royal College of Physicians, and the Honorary Fellowship of the Royal Society of Medicine.

Fulton married at Oxford in 1923 Lucia Pickering Wheatland, of Salem, Massachusetts, who survives him. Their many friends in all countries, and especially in Britain, will mourn the early death of one whose work lives on, not only in his massive contribution to medical literature and in the institutions to which he gave so much of himself, but in the work of others whose debt can never be fully acknowledged.—F. N. L. P.

We are indebted to Sir ARTHUR MACNALTY for the following appreciation: I am grieved to hear of the death of John Fulton. When the news came, I had just received a letter from him enclosing his tribute to the memory of our friend, W. W. Francis (*Journal of the History of Medicine and Allied Sciences*, 1960, xv, No. 1), and saying with his wonted kindness that he was sending me a two-volume set of Henry Sigerist's essays on the history and sociology of medicine. He also asked for some medical historical papers which I was about to send him.

The pupil of Sherrington and of Harvey Cushing, Fulton became a great neurophysiologist. Sherrington was proud of his researches in this field, and collaborated with him. I remember he expressed his delight when in 1931 his disciple was appointed to the professorship of physiology at Yale. Of Fulton's enduring work there in research on the central nervous system and as a teacher others will speak. Let me say something here of John Fulton, the medical historian.

I first met Fulton when I was staying at 13, Norham Gardens, Oxford, in 1921. Lady Osler took me into her late husband's library, saying, "I want you to meet one of our Rhodes scholars whom William would have loved." There sat a young undergraduate who was being shown some of the treasures of Osler's collection by Dr. W. W. Francis. It was a historic occasion. Osler's influence pervaded the room; and the wish to collect medical books and to share knowledge of them was then created in the mind of the future Sterling professor of the history of medicine. Fulton's interest in the subject was also fostered by Harvey Cushing and by Sherrington, a collector of *incunabula*. From this first meeting Fulton and I were friends.

In 1941, when I was appointed editor-in-chief of the *United Kingdom Medical History of the Second World War*, Fulton at once got into touch with me, for at that time he had been invited to undertake a similar task for the Official American Medical History of the War. We discussed the planning of the two histories and exchanged information and copies of early draft contributions. Ultimately, the United States Government decided that the responsibility for the Official History should be undertaken by the Medical Department of the United States Army, as had been the case with the Medical History of the first world war. This was a disappointment to Fulton, but he bore it with equanimity. His work on the history was not wasted, for it proved of value to the Army historians. The change was probably a blessing in disguise, for Fulton's health was not good, and time was given him to write his masterly biography of Harvey Cushing, to bring out Cushing's *A Bio-Bibliography of Andreas Vesalius* and other works, and to see his library and department of medical history established in Yale University. In sickness and health and in his work he was much helped by his devoted wife.

Fulton owed allegiance to three great universities—Harvard, Oxford, and Yale—and of each was a loyal son. In spite of ill-health he made a superhuman effort to visit Oxford to receive the honorary degree of which he was so proud.

This account would be incomplete if nothing were said of Fulton's character. He was essentially a good man. Virtue went out of him to help others, not only in the study of neurophysiology and of medical history, but also in the perplexities and vicissitudes of life. That is why his students loved and revered him, and why he had countless friends and correspondents on both sides of the Atlantic. The love of mankind and of books was with him to the end. John Fulton sought truth alike in physiology and in the history of medicine. He was Valiant-for-truth, and we can be sure that when he passed over all the trumpets sounded for him on the other side.

ESTHER M. KILLICK, D.Sc., M.B., Ch.B., M.R.C.P.

Professor Esther Killick, professor of physiology at the Royal Free Hospital School of Medicine, died suddenly in hospital on May 31, at the age of 58.

Esther Margaret Killick, the daughter of Dr. Arthur Killick, was born on May 3, 1902. She was educated at Leeds Girls' High School and the University of Leeds, where she graduated M.B., Ch.B. in 1929. She took the M.R.C.P. in 1931 and the degree of D.Sc. at Leeds in 1952. From 1929 to 1935 she worked in the department of physiology at Leeds as physiological investigator to the Safety in Mines Research Board. At this time she did her classical work, some of it in collaboration with the late Professor J. S. Haldane at Birmingham, on acclimatization to carbon monoxide. Her interests widened to include the clinical and applied aspects of respiratory physiology during the period from 1935 to 1941 when she was successively lecturer in industrial medicine and hygiene in the University of Birmingham and lecturer in applied physiology at the London School of Hygiene and Tropical Medicine. In 1938 she married Arthur St. G. Huggett, F.R.S., professor of physiology at St. Mary's Hospital Medical School.

Esther Killick was appointed Sophia Jex-Blake professor of physiology at the Royal Free Hospital School of Medicine in 1941. Thereafter she carried her full share of the load of teaching and of college and university administration inseparable from tenure of a London chair, as well as playing an active part in the affairs of the Physiological Society, on whose committee she served from 1944 to 1948. Nevertheless she continued her own research work, and it is an indication of her sustained interest in haemo-respiratory problems that her last paper in the *Journal of Physiology* was a detailed analysis of the resuscitation of animals from acute carbon-monoxide poisoning. She continued, too, to

give invaluable help in the application of physiological knowledge in this field by her membership of official committees on breathing apparatus and resuscitation, and of the National Coal Board's physiology advisory panel, of which she was chairman. She also served on the Coal Gas Poisoning Subcommittee of the Science Committee of the B.M.A.

Esther Killick was a person of rare intellectual and moral integrity. Acute powers of critical judgment and a fine clarity of thought and expression were in her allied to quiet charm and a real if uneffusive kindness. To those who enjoyed the privilege of her friendship, which she did not bestow indiscriminately, she was generous and utterly loyal. By her untimely death London University has lost a distinguished teacher, and physiology in this country is the poorer. Her colleagues and friends will feel deep sympathy with her husband and their two daughters.

A colleague in Professor Killick's department writes: The sudden death of Professor Killick has come as a great personal loss to all of her colleagues, and especially to every member of her staff. Calmly, and without apparent emphasis, her integrating influence was exerted at all times in a department in which many workers pursue their own individual research projects. While herself actively engaged with her own team on work on resuscitation from carbon-monoxide poisoning, and in spite of numerous outside engagements and the calls of teaching, she would always give a sympathetic hearing and unhurried advice whatever the problem might be. Her own standards of laboratory method and thought were evident at the research seminars which she had instituted in the department, and her wide knowledge of physiology and biochemistry came to the fore. Colleagues, and generations of students, realized that the professor's opinion was based on a thorough knowledge of school and university regulations and lore. Besides her remarkable administrative ability, her personal guidance, and her friendly nature will be sorely missed in the department by both research workers and technical staff alike.

F. A. DENZ, M.D., M.Sc.

Dr. F. A. Denz, associate professor with charge of chemical pathology in the medical school of the University of Otago, Dunedin, died there on May 14, at the age of 51.

Frank Anton Denz was born on September 4, 1909, in Pokeno, New Zealand. After working in the Department of Agriculture, Wellington, for six years, during which time he obtained the degree of M.Sc. with first-class honours in chemistry, he was stimulated to seek wider fields for his activities by a general cut in Government salaries. He reached London in 1933 with the intention of going to Manchester to work for a research degree in chemistry. A chance meeting with an old friend turned his mind to medicine, and he entered University College Hospital as a student. Supported by his own exertions as a coach and teacher of chemistry, together with the help of his wife, who had joined him from New Zealand, he completed the medical course, qualifying in 1939 and graduating M.B., B.S. in 1941.

After three house appointments he joined the R.A.M.C. and soon became a specialist pathologist, serving as a major in North Africa, Italy, Belgium, and Germany. After demobilization he obtained a registrar appointment in Professor (now Sir Roy) Cameron's department. In this favourable environment his talents as an experimental pathologist soon became evident. In 1947 he joined the recently formed Toxicology Unit of the Medical Research Council, and remained with it first at Porton and then at Carshalton until 1953. A steady output of papers on a variety of topics reflected his industry, versatility, and capacity as an experimenter.

In 1953 he was invited to return to New Zealand and was offered the opportunity of setting up a toxicology unit in Dunedin under the auspices of the New Zealand Medical Research Council. The decision to leave this country was not made easily, but there was clearly a need for work in his own country on the toxicology of food additives. During the next years his advice was constantly sought on a variety of problems connected with the broad subject of toxicology. In 1957 he was a member of a W.H.O. Expert Committee on Food Additives meeting in Geneva, and in the following year he was invited to visit the U.S.A. In 1959 he was appointed associate professor of pathology with charge of chemical pathology at Dunedin. He had hardly started when illness overtook him. After an operation which he knew had not been successful, he struggled on with characteristic courage for a few more weeks until his final illness. Our sympathy is extended to his widow and four children.

J. M. B. writes: Frank Denz and I worked in close collaboration for six years. His loyalty and capacity for hard work made him an invaluable colleague and friend. He delighted in argument, never hesitating to provoke one by propounding some heresy if he felt a discussion needed brightening up. His outspokenness and love of "debunking" may have upset some people, but those who worked with him valued it highly because his real interest lay in getting at the truth. He had had to work hard all his life to get what he wanted, but he appeared to have enjoyed every moment of it, and leaves a host of friends in all walks of life who mourn his passing. His return to New Zealand in 1953 was a sad loss to the small band of experimental pathologists in this country, and, as he had predicted, his output of scientific work diminished because of the number of other responsibilities that came his way.

Meeting him again in 1957 at a World Health Organization committee in Geneva, I soon saw that he had lost none of his fire in argument. He visited the U.S.A. in the following year, and I learnt subsequently that his vitality had impressed all those he had met, and they were very upset to hear of the serious nature of his illness a year later.

R. C. MUIR, M.B., Ch.B., D.P.H.

Dr. R. C. Muir, who had practised for many years in Leeds, died there on April 13. He was 76 years of age.

Robert Charles Muir was born on February 13, 1884, and studied medicine at Glasgow University, graduating M.B., Ch.B. in 1907. After holding a resident appointment at the Bradford Children's Hospital, he became senior resident medical officer at the Leeds Public Dispensary. After obtaining the D.P.H. at Liverpool in 1912, he settled in general practice in Leeds. During the first world war he served in the R.A.M.C. in India and Salonika, attaining the rank of major. After demobilization he returned to his practice in Leeds, where he became also honorary pathologist to the Leeds Public Dispensary and honorary medical officer to the Meanwood convalescent home. A general practitioner of the old school, he was completely absorbed in his work, and possessed a strong sense of duty. With his quiet manner and keen sense of humour, he was loved and respected by all his patients. He leaves a widow, to whom the sympathy of all who knew him will be extended.

Dr. ARTHUR SHEARD writes: Robert Charles Muir was essentially an individualist. My long association with him as a colleague in medical practice (he disliked the word "partner," which to him savoured of commercialism) fostered an increasing admiration and respect for his keen intellect, his sound clinical judgment, his professional and personal integrity, and his constant concern and consideration for the welfare of his patients. He devoted the whole of his time and energy to their interests, not only in medical matters but also in the wider sphere of their personal, domestic, and social problems. He inspired confidence, and was regarded with universal esteem and affection.

His penetrating mind, often livened by flashes of dry humour, sought the crux of each problem, which he illumined with a wise philosophy. I recall one occasion when we both felt sad and frustrated by the tragic death of a patient who had failed to report a vital symptom until too late. He reminded me of the many others whose trust and confident co-operation had carried them triumphantly through the storms of adversity, and concluded with the cryptic remark,

"Our patients always get the treatment they deserve, even if they do not always deserve the treatment they get." He also used to say that "only half the illness in the world is unavoidable. The other half is due to ignorance or folly, or both." He maintained a sympathetic tolerance of the beliefs and an understanding of the frailties of others. He found time to explain to his patients the nature of their ailments and how they could help themselves in promoting a cure. He would often tell them, "The healing art is 90% common sense salted with 10% knowledge."

He has gone from us, but his ideals live on.

FRANCIS FRIEND, M.D., D.M.R.E.

Dr. Francis Friend, consultant radiologist to St. Albans City Hospital, died in that hospital on April 24, aged 60.

Franz Freund (he changed his name to Francis Friend in 1947) was born in Vienna on November 8, 1899, and graduated in medicine at the university there in 1925. Two years later he was appointed assistant to Professor Holzknecht and took part in the research and teaching for which the Holzknecht Institute was internationally famous. He published papers at this time on the histobiology of radiation, and was specially interested in the origin of the wandering cells, holding with Paul Grawitz that migratory cells originate locally. In 1934 he was appointed radiologist to the Vienna transport services. Pulmonary tuberculosis was then rife, and its early diagnosis was a serious problem. Because of an early belief that this infection started only in the apex of the lung, radiographic examination was confined to this region. Dr. Friend emphasized the need to radiograph the whole of both lungs, and his efforts in improving early diagnosis led to a marked reduction in mortality. He contributed to discussions on pulmonary tuberculosis at international congresses at Zurich, St. Moritz, and London, and published a number of papers, the last in 1959.

After the Nazi occupation of Austria in 1938 he left for England, being one of a group of 50 Austrian doctors admitted by special permission of the Home Office. He was given a place at St. Bartholomew's Hospital, and took the Conjoint qualification in 1941 and the D.M.R.E. of Cambridge in the following year. Later he served in the Emergency Medical Service as radiologist at the Royal National Orthopaedic Hospital, Stanmore. After the war he was appointed consultant radiologist to the City Hospital, St. Albans, the Manor House Hospital, Golders Green, and the Hendon Isolation Hospital. He held these appointments until two and a half years ago, when illness forced him to retire.

Dr. Friend was a man of culture and widely read. His native land always held a special place in his affections. Friendly and quiet in disposition, he had a gentle personality. The vicissitudes of this troubled age profoundly changed his life, but did not defeat him. We shall remember with affection and gratitude a man who achieved success and distinction in both Austria and England. He leaves the world the better for his work and presence.—E. J. E. T.

R. B. EDWARDS, M.B.E., M.B., B.S.

Dr. R. B. Edwards, who practised in Mold, Flintshire, for more than 40 years, died after a long illness at his home in Mold on May 19. He was 75 years of age.

Roger Bellis Edwards was born on February 21, 1885. He was the son of Dr. David Edwards and grandson of the Rev. Roger Edwards, a noted contemporary and friend of Daniel Owen, the great Welsh novelist. From Mill Hill School Roger Edwards went on to study medicine at Liverpool University, where he was president of the Students' Union and captain of the university rugby team. Qualifying in 1910, he graduated M.B., B.S.(London) in 1911. He joined his father and the late K. V. Trubshaw, F.R.C.S., in practice in Mold, becoming the senior partner in 1919. He retired from practice in 1955 after a combined service in Mold with his father of over 80 years.

Roger Edwards was a former chairman of the Denbigh and Flint Division of the B.M.A. and a former president of the North Wales Branch, county court medical referee, and medical officer to Mold Red Cross Detachment. He was awarded the M.B.E. for his work in the Leeswood Hall Hospital during the first world war. He was appointed High Sheriff for Flintshire in 1957. "Dr. Roger," as he was affectionately known, was greatly loved by all his patients and will be sadly missed in his home town.

His first wife died in 1956, and he is survived by his second wife and two sons of the first marriage.—J. B. D.

A. C. L. O'S. BILDERBECK, M.B., B.S.
D.P.H., D.T.M.&H.

Colonel A. C. L. O'S. Bilderbeck, who had had a distinguished career in the Indian Medical Service and elsewhere, died at his home at Bexhill-on-Sea, Sussex, on April 5. He was 73 years of age.

Alured Charles Lowther O'Shea Bilderbeck was born on August 22, 1886. Educated at Clifton College and Christ's College, Cambridge, he went on to St. Bartholomew's Hospital with a Jefferson entrance exhibition, and graduated M.B., B.S. from London University in 1913. He obtained the Cambridge D.P.H. in 1920, and the D.T.M.&H. of the English Royal Colleges seven years later. In 1914 he entered the Indian Medical Service, and was posted as medical officer to the 2/6 Gurkha Rifles, a regiment with which he was to serve for many years. He took part in operations on the North-West Frontier before the first world war, and in Mesopotamia in 1916–17, being mentioned in dispatches for gallantry at the battle of Ramadi in 1918. After serving in Persia in 1920–1, he was assistant director of public health in Burma for six years, at first with the rank of major and then lieutenant-colonel. Later he was port health officer and civil surgeon at Aden, and then port health officer at Bombay, where he served for ten years. He was the author of *The A.R.P. Instructor's Manual* (1937), the use of which was officially adopted throughout India and Burma. He conducted courses on air-raid precautions in Bombay, and for these services was appointed an Officer of the Venerable Order of St. John of Jerusalem in 1940.

Reverting to the military department of the I.M.S. in 1939, he took part in two operations in the North-West Frontier, and was mentioned in dispatches in 1941 and 1942. From 1941 to 1943, when he retired, he was assistant director of medical services in the Madras District. Re-engaged during 1944–5, he was deputy surgeon-general for air-raid precautions in Bengal. Returning to the United Kingdom in May, 1945, he went to Germany with the R.A.M.C. in the following December, subsequently transferring to the Control Commission for Germany as principal control officer in the health department in Schleswig-Holstein and, later, Hamburg. On relinquishing the appointment in 1950 he received the Danish Red Cross Medal for his co-operation with the Danish Red Cross in its German refugee relief work. For several years afterwards he gave lectures on first aid in Bexhill. He leaves a widow, one son, and one daughter.

Sir ROBERT McCARRISON, C.I.E., M.D., D.Sc.
LL.D., F.R.C.P.

The obituary of Sir Robert McCarrison was published in the *Journal* of May 28 (p. 1663).

Professor A. D. GARDNER writes: Although I had known of Sir Robert McCarrison's pioneer work on nutrition ever since my student days, I had not come into any close contact with him until 1948, when I became his nominal overseer in his last salaried post, that of chairman and director of postgraduate medical education in Oxford. Before taking

this post he had, since 1944, been a most energetic and successful regional adviser to the Emergency Medical Service and had been entrusted by the Ministry, with the University's agreement, with the local management of the postgraduate scheme for demobilized medical officers.

The post he took up in 1948 was none too easy a post, falling as it did in a kind of no man's land between an apathetic university and a Ministry struggling with all the novelties of the National Health Service. Among the novelties was the principle that the old University should abandon its age-long exclusive universality and undertake the parochial duties of a regional medical centre. Moreover, any growth of clinical medical studies was looked on askance by most Oxford seniors. However, the task of building something worth building against indifference or opposition and with inadequate means was exactly in Sir Robert's line; and even more in his line was the guidance and mothering of young men and women graduates in their efforts to get a good postgraduate training. He was indefatigable (at 70–75 years of age) in visiting all the major hospitals of the region to assess the pre-registration posts they could provide; and his great powers of persuasion induced the medical staffs to organize refresher courses for general practitioners.

His home life was made happy by his devoted wife and by equally devoted helpers; and his misfortunate lack of children was compensated by a general "uncle-ship" to all the little ones of his neighbours. A regular churchman, he was churchwarden of his parish church, St. Andrews, where he read the lessons, as I am told, beautifully. There was indeed a touch of unworldliness in his nature; he knew more about nutrition and less about income-tax than anyone I have met.

For a man to be superlatively good at research, lecturing, clinical medicine, administration, and the guidance of the young must be one of the rarest coincidences, while at the same time to be humorous, modest, and kind must be even rarer. In him we have lost one of the most attractive and outstanding medical figures of our time.

Medico-Legal

INFAMOUS OR DISGRACEFUL CONDUCT

[FROM OUR LEGAL CORRESPONDENT]

Judgment in the first appeal to the Judicial Committee of the Privy Council from the Disciplinary Committee of the General Dental Council under the Dentists Act, 1957, was delivered on May 11 (*The Times*, May 12). The appeal was successful.

The judgment is of considerable importance to the dental profession, as it construes the words "infamous or disgraceful conduct in a professional respect" in Section 25 of the Dentists Act, 1957: it is of interest to the medical profession because of the similar (but not identical) words in Section 33 of the Medical Act, 1956. These two sections provide that practitioners be struck off the register if convicted of a crime falling within certain limits (which differ in each profession). The two sections then deal with striking off for other misconduct: a dentist is liable to be struck off if he has been guilty of "*any infamous or disgraceful conduct in a professional respect*": a medical practitioner may be struck off if he is found to have been guilty of "*infamous conduct in any professional respect.*"

Facts of Dental Case

The appeal in this case was brought by Mr. Dudley Ernest Lyncoln Wager Felix, aged 29, a native of Sierra Leone, and a dentist registered under the Dentists Act, 1957. The appeal was from a determination of the Disciplinary Committee that he had been guilty of infamous or disgraceful conduct in a professional respect.

The charges against Mr. Felix concerned, firstly, overcharging, and, secondly, wrongful certification. The Disciplinary Committee found that Mr. Felix had wrongfully charged for three fillings which had not been done (involving a total of £5 7s. 7d.). His case on these charges was that he admitted the overcharging but denied that it was done with any fraudulent or dishonest intent: it was simply due to carelessness. The Disciplinary Committee also found that Mr. Felix had wrongfully certified that 16 fillings were required when in fact 13 of them were unnecessary. Mr. Felix admitted making the certificate, but it was not disputed that he had done three of the fillings, and he throughout contended that 10 old fillings were defective and needed replacement, and the other three were suspect. Although not explicitly stated in the Disciplinary Committee's findings, the Judicial Committee considered that the Disciplinary Committee must be taken to have accepted the appellant's explanation of overcharging as true, and to have found that the certificate concerning the 16 fillings was based on an honestly held opinion. The question therefore arose whether, on those facts, the conduct of Mr. Felix was "infamous or disgraceful conduct" within the proper interpretation of those words in the statute.

"Infamous" and "Disgraceful" Construed

Any words in a statute are prima facie to be considered in their natural and ordinary meaning. The Judicial Committee therefore turned to the *Oxford English Dictionary* for guidance in this hitherto uncharted statute. Under "infamous" they read the meaning:

> "2. Deserving of infamy; of shameful badness, vileness, or abominableness; of a character or quality deserving utter reprobation,"

and under "disgraceful" they read,

> "2. Full of, or fraught with, disgrace; that brings disgrace upon the agent; shameful, dishonourable, disreputable."

Although the words "infamous or disgraceful conduct" have to be construed in conjunction with the words "in a professional respect," the Judicial Committee considered that the two adjectives remained as words denoting conduct deserving of the strongest reprobation, and indeed so heinous as to merit, when proved, the extreme professional penalty of striking off. They held that to make such a charge good there must, generally speaking, be:

> "Some element of moral turpitude or fraud or dishonesty in the conduct complained of, or such persistent and reckless disregard of the dentist's duty in regard to records as could be said to amount to dishonesty for this purpose."

The appellant's conduct did not fall within this scope, and therefore his appeal was allowed and the General Dental Council ordered to pay the costs of the appeal.

Comparison with Medical Acts

The authorities construing the words "infamous conduct in a professional respect" in the statutes successively regulating the medical profession (now in the Medical Act, 1956) reach a rather different conclusion. Although it was generally thought that the words in the Dentists Act would be construed in much the same way as the words in the Medical Act,[1] the Judicial Committee adopted a different construction. The *locus classicus* on the medical statutes, to which the Judicial Committee was referred, is Allison *v.* General Council of Medical Education and Registration.[2] Lord Justice Lopes put forward the following definition:

> "If it is shown that a medical man, in the pursuit of his profession, has done something with regard to it which would be reasonably regarded as disgraceful or dishonourable by his professional brethren of good repute and competency, then it is

[1] *Halsbury's Statutes of England*, vol. 37, p. 697 note.
[2] [1894] 1 QB 750.

open to the General Medical Council to say that he has been guilty of infamous conduct in a professional respect."

Lord Esher, in the same case, adopted this definition, and added:

"The question is, not merely whether what a medical man has done would be an infamous thing for anyone else to do, but whether it is infamous for a medical man to do. An act done by a medical man may be infamous, though the same act done by anyone else would not be infamous."

The difference between this construction of the Medical Act and the present construction of the Dentists Act is best seen in the professional offence of advertising. In a case of this sort, Lord Justice Scrutton defined "infamous conduct" as being merely "serious misconduct in a professional respect." He said,[3]

"It is a great pity that the word 'infamous' is used to describe the conduct of a medical practitioner who advertises. As in the case of the Bar so in the medical profession advertising is a serious misconduct in a professional respect and that is all that is meant by the phrase 'infamous conduct'; it means no more than serious misconduct judged according to the rules written or unwritten governing the profession."

If the definition of the Judicial Committee in the present case is applied as being all-embracing, then a dentist could only be struck off under Section 25 for advertising if his advertising amounted to such a disregard of his duty as a dentist as to amount to dishonesty. (The position as regards the Medical Act is, of course, not affected by this decision.) There is a considerable difference here, though it is a difference of degree. Possibly the practical effect of the difference will not be very great, since practitioners are in any case only struck off for very serious breaches: it is noteworthy, however, that a submission, based on this decision, that there was no evidence of infamous or disgraceful conduct on charges of overcharging (amounting to £72) was upheld by the Disciplinary Committee of the General Dental Council on May 12 (*The Times*, May 13).

[3] R. *v.* General Medical Council [1930] 1 KB 562 at 569.

Medical Notes in Parliament

DOWNWARD TREND OF STRONTIUM-90 LEVELS

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Mr. JOHN MORRIS (Aberavon, Lab.) waited until two o'clock in the morning of June 1 to ask some questions about the Second Report of the Agricultural Research Council on the amount of strontium-90 in milk and other agricultural products*; and to hear Miss EDITH PITT, Parliamentary Secretary to the Ministry of Health, say half an hour later that there was no reason to be alarmed about current levels so far recorded, and that the trend was downward and should continue so unless nuclear air tests were resumed.

Questions not Hysterical

Mr. MORRIS disclaimed any intent to adopt a hysterical tone, but asked that in view of the unexpectedly rapid increase since 1954 in the amount of contamination in food, the soil, and human and animal bones, the public should be given some reassurance. The key part of the report was the statement that

"It appears that the 12-month mean of contamination of milk [for England, Wales, and Scotland] increased by 40% between December, 1958, and June, 1959. The values rose relatively steadily during the intervening period, but such information as is available for samples collected after June, 1959, shows that the values have since decreased."

*See *British Medical Journal*, April 9, p. 1117.

He asked what was the position to-day, and if the trend had continued. The increase of 40% in the relevant months was caused by the testing of nuclear weapons in the northern latitudes between November, 1958, and May, 1959. There had been a cessation of those tests. What was the present situation? The report also stated:

"It may therefore be assumed that no further increases in the levels of strontium-90 in milk are to be expected if weapon trials are not resumed and the rate of fall-out consequently continues to decrease."

That was a reassuring statement, and he hoped it would be brought to the notice of the Prime Minister to show how vitally important it was that every possible pressure should be brought to bear on the necessity for ceasing tests.

Is Safety Threshold a Pious Hope?

Another question was whether the key factor in the contamination of milk and other products was recent deposition or accumulative deposition. The report did not come down firmly either way. It suggested that evidence tended to the view that it was recent deposition, but there was a lack of complete evidence; and it stated that the committee had not the whole answer and would like more evidence. He asked the Government to explain the significance of the figures given in the report. Were they at present a hazard? One school of thought suggested that any contamination was dangerous; that the relationship was linear, and that the number of cancers increased directly with the amount of strontium-90. Another school thought there was a threshold of safety. The Medical Research Council stated that this was 100 units, that this level must not be exceeded, and that if it rose much above 10 units it should be a matter of immediate consideration. What was the correct view? It would be a great reassurance to the public if it could be scientifically established that there was a threshold of safety; or was that merely a pious hope of the Medical Research Council? He understood that the Council intended soon to produce a White Paper on the spread of the hazard and its possible effects, and he asked if the Parliamentary Secretary could indicate when the White Paper would be issued.

Government's Monitoring Programme

Miss PITT said in reply that the experts were emphatic that the present levels of strontium-90 in milk were no cause for alarm or concern. There was no complacency on the part of the Government about the dangers of fall-out. They had an effective monitoring programme planned and supervised by an expert subcommittee of the Agricultural and Medical Research Councils and the Development Commission. The efficacy of the programme depended on careful statistical design which ensured that samples were truly representative, and on the accurate measurement of small amounts of radioactivity. Statistical design was particularly important in the monitoring of food, which contained over 90% of the strontium-90 which entered the human body in the United Kingdom.

It was understandable that the Welsh authorities would themselves like to take samples and assess them independently, as Mr. Morris had suggested, but the argument overlooked the independent, authoritative nature of the research councils from which the Government got advice. There were other arguments against it. Surveys should cover the pattern of production and consumption of food, so that statistically valid sampling schemes could be designed. It was much cheaper in time and effort for data covering the whole country to be considered together. Elaborate analytical procedures were necessary to detect strontium-90 in the minute quantities at present found in human diet.

It was much more efficient and economical to do the work in relatively large laboratories where the skilled directing staff could be properly used. The present organization of

survey work co-ordinated results so that the general situation could be assessed by the Medical Research Council. This overall assessment would be much less easy if part of the work were carried on on a regional basis. In international discussions the British plan had been held up as a model for all nations to copy because of the excellence of its statistical design. There was no call for a special expense in monitoring, nor could it be argued that Wales did not get a fair share of the fall-out monitoring programme.

Variation with Local Rainfall

Deposition of strontium-90 varied more or less with local rainfall, and therefore the general level for Wales was above the national average—another point mentioned by Mr. Morris. Local variations in deposition might at present levels be ignored for all practical purposes. The position could be summed up in the address given by Dr. R. Scott Russell to the National Farmers' Union at Beaumaris on May 11, in which he said: "We could say that man's increased exposure to radiation from strontium-90 was comparable to that which, unknowingly, many people had accepted down the ages by moving from one district to another."

The proportion of strontium to calcium transferred from diet to human bone was only about one-quarter of the proportion of strontium to calcium in the diet. This fact should be emphasized, because it was not generally realized. In 1956 the Medical Research Council expressed the view that the level of strontium-90 in human bone should not exceed 100 units; and that if the level showed signs of rising greatly beyond one-tenth of this value—i.e., 10 strontium units—it would be desirable to give immediate consideration to it.

Latest Figures

The most recently published measurements indicated that the average levels were well below these figures. The Medical Research Council was undertaking a further comprehensive assessment of the significance of all the available evidence on the exposure of man to ionizing radiations, which would include an appraisal of the effects of the radioactive contamination of food by fall-out. On the latest figures, for which Mr. Morris had asked, she stated that the report for the second half of 1959 was in preparation and should be available within the next month or two. On the question whether contamination was caused by cumulative effect or by recent falls, she said she was advised that it was predominantly by recent falls. The latest figures were not yet published, but they showed that the trend was downward and that this was expected to continue. On the question of the elimination of milk from the diet, the most recently available figures gave no indication that any alteration should be made to the diet of children on account of the contamination of milk from radioactive fall-out. Although milk was the main source in the diet of strontium-90 from world-wide fall-out, the suggestion that for this reason it presented a special hazard was incorrect. Hazard was best measured in terms of the ratio of strontium-90 to calcium in the diet as a whole, and if milk were removed the calcium which it provided would have to be obtained from some other source unless the diet was to be seriously impaired. The resulting ratio of strontium-90 to calcium in the diet would be unlikely to be greatly changed. While this was a matter which should be, and was being, carefully watched, there was no reason to be alarmed about any current levels in milk so far recorded.

The simple truth was that the level was still so low that there was no ground for immediate consideration; that the trend was downward and should continue so unless air tests were resumed; and that it was so small that local variations—for example, between Wales and East Anglia and Cumberland—could for practical purposes, though not for scientific analysis, be ignored.

IMPROVEMENTS IN FLAME-RESISTANT MATERIALS

[FROM OUR PARLIAMENTARY CORRESPONDENT]

An appeal by Mr. GEORGE CRADDOCK (Bradford, South, Lab.) for fuller Government support in publicizing the sale and use of non-flammable materials, made in a short adjournment debate on May 30, was met by a statement from the Board of Trade spokesman that the public response so far to the use of specially processed materials had been bitterly disappointing and negligible. At the same time he held out the prospect of new developments which eliminated the adverse effects on the "feel" of fabrics resulting from existing methods of processing; and he refused to believe that parents were not prepared to pay the few shillings' additional cost involved.

Over 1,500 Deaths Annually

Mr. Craddock said there was a mounting toll of injury and death, much of which could be avoided, from burning accidents in the home. According to the British Safety Council an average of 1,500 people died and over a million were injured each year. The interim report of the Committee on Consumer Protection stated that suggestions that the use of flame-resistant fabrics should be a statutory requirement, at any rate in certain forms of clothing—e.g., children's nightwear—made "some appeal." He mentioned particularly the research undertaken by Proban Ltd., which had resulted—at a total cost of £306,000—in the development of a process by which winceyette could be made non-flammable and safe for children.

Public Response "Bitterly Disappointing"

Mr. JOHN RODGERS, Parliamentary Secretary to the Board of Trade, said there were now textile fabrics which in their natural state seemed to meet the requirements specified last year in the Fabrics (Misdescription) Regulations for fabrics claiming to be flame-proof or flame-resistant. The heavier woollen fabrics, nylon, Terylene, and one or two others might do so. But this was not necessarily so if there was a blend or trimming of other fabrics, or if certain finishes were applied. Unfortunately these were not materials which parents usually chose for children's nightwear. A leading firm making man-made fibres had on test a fibre which he understood was highly flame-resistant. They expected to have it on the market in a year if the tests proved successful. It was claimed that it would revolutionize the whole problem of providing flame-resistant clothing. Mr. Craddock had referred to the Committee on Consumer Protection, but they had been unable to recommend compulsion at this stage. There were three processes available which could render certain fabrics flame-resistant to the degree mentioned in the Fabrics Regulations. The companies concerned had devoted much time and money to their development, and the materials treated by these processes had been handled by retailers in a manner which should have provided a fair test of demand. But the public response was bitterly disappointing—"negligible" was the only word to describe it. The explanation was said to be that the treatment made the cloth hard or harsh to touch, and that the treated fabrics were more expensive.

There had been a further technical development, at least in one of the processes, Proban, which it was claimed virtually eliminated the adverse effect on the "handle" of the cloth. If that was so, there remained only the question of price. His information was that what the processes added to the cost of a nightgown for a small child was approximately the price of 20 cigarettes. Adopting an evening paper headline, "Is four shillings too much for safety?" he asked, "Is it? Are we to think that parents set no higher value than that on their children's lives?" He found it hard to believe. Only those who did not appreciate the dangers could begrudge this expense.

Propaganda Among Mothers Needed

The task, therefore, was to educate, to conduct a propaganda campaign. He would like to see some way in which the Government could help, instead of standing on the sidelines and cheering others on. He did not accept as a right use of taxpayers' money expenditure on an advertising campaign to persuade people to ask for flame-proof or flame-resistant fabrics. But he was attracted to the idea of a special campaign warning mothers of the dangers and apprising them of the availability of these new finishes, and possibly new fibres which might come on the market. He hoped that one of the results of the discussion would be that all concerned in the manufacture, use, and sale of these fabrics would seriously consider the possibility of such a campaign. If it was to be effective it was essential that these garments should be stocked widely. One large chain store had accepted the new Proban process as satisfactory and had placed an order for several thousand yards, and hoped to have nightdresses made from it on sale before long. He would also ask the Committee on Consumer Protection to consider whether any special steps were required to mark merchandise as being flame-proofed.

DEBATE ON HOMOSEXUALITY

Mr. KENNETH ROBINSON (St. Pancras North, Lab.), who won first place in the ballot on May 31 for the right to choose a subject for debate on June 29, gave notice that he would call attention to Part II of the Wolfenden Report, dealing with homosexuality, and move a resolution.

NEW STATUTES

The Royal Assent was signified by commission on June 2 to the Indecency with Children Act, the Radioactive Substances Act, and the Royal College of Physicians of London Act.

QUESTIONS IN THE COMMONS

Emergency Night-call Services

Mr. L. PAVITT (Willesden, West, Lab.) asked the Minister of Health on May 30 how many cities and towns now had emergency night-call services offering to deputize for general practitioners; how many of these were on a purely commercial basis; and how many were under the control of the local executive council. Miss EDITH PITT, Parliamentary Secretary, stated that there was no centrally available information regarding the numbers and types of deputizing services, but she had no reason to suppose that such services were operating on a commercial basis in more than a very few areas. Deputizing services were not controlled by executive councils, and most of them were personal arrangements between doctors.

Foods Standards Committee

The Minister of Agriculture, Fisheries, and Food announced on May 30 the names of the reconstituted Food Standards Committee. The chairman is Mr. R. Groves, Master of Dulwich College. The other members are:

Trade Members.—Mr. Colin S. Dence (managing director of Brand and Co. Ltd., a past president of the Food Manufacturers' Federation); Mr. A. Glover (head of research department, Co-operative Wholesale Society Ltd.), and Mr. E. W. Graham Guest (a director of MacVitties Guest and Co. Ltd., of Edinburgh).

Scientific Members.—Professor B. S. Platt (director of the Human Nutrition Research Unit, Medical Research Council), Mr. R. W. Sutton (public analyst for the County and County Borough of Derby), and Mr. P. McGregor (representing the Government Chemist's Department).

Independent Members.—Mr. C. A. Adams (a past vice-president of the Society of Public Analysts; former assistant-secretary, Ministry of Food (now retired)); Mrs. M. Carroll-Marx (housewife; head of the food department, W.V.S.), and Mr. J. A. O'Keefe (head of the public control department of the Middlesex County Council).

Universities and Colleges

ROYAL COLLEGE OF SURGEONS OF EDINBURGH

At a meeting of the College, held on May 6, with Professor John Bruce, President, in the chair, the following candidates who had passed the requisite examinations were admitted Fellows:

J. G. Allman, J. H. F. Batstone, N. Bhaduri, W. H. Bisset, D. G. Calvert, K. Chambler, R. G. Clark, M. Cohen, B. C. Cohney, D. H. Coop, Delia M. H. H. Cothay, C. N. Dedhia, E. E. Denman, H. C. De Wet, M. M. I. Fakhr, A. D. George, Mavis G. Gilmour (née Holness), P. Gortvai, P. S. Grewal, J. M. S. Hague, M. A. Henderson, W. H. Huffam, K. F. Hume, E. G. Ibach, J. D. Iswariah, T. E. Jeffreys, C. O. R. King, W. J. Laister, G. J. Little, P. Mactaggart, D. J. McWilliams, H. Makki, G. B. Markey, B. C. Meehan, B. V. Mehta, J. M. Mistry, R. N. Mullick, G. A. I. Namsoo, C. H. Ng, J. A. O'Reilly, W. McN. Orr, P. M. Paulose, V. G. Phansalkar, W. J. Poate, L. W. Poole, A. A. Qazi, R. A. Rivett, J. S. Scougall, D. K. Sutton, C. Y. Tan, D. S. Thomson, J. B. Wedande, S. B. Williams, K. H. Yeoh.

UNIVERSITY OF ABERDEEN

Dr. Grace C. Turner has been appointed to a terminable Lectureship in Bacteriology from September 1, 1960.

UNIVERSITY OF LONDON

The title of Reader in Human Metabolism in the University has been conferred on Dr. Victor Wynn in respect of his post at St. Mary's Hospital Medical School.

UNIVERSITY OF SHEFFIELD

At a meeting of the University Council on May 20 appointments were made as follows: Dr. R. B. Bradshaw and Dr. J. Bullock, full-time Demonstrators in Anatomy; Dr. W. H. I. Shedden, full-time Assistant Lecturer in Bacteriology; Dr. R. L. Hunt, part-time Clinical Teacher in Obstetrics and Gynaecology; and Dr. Anne E. Walker, Boots Medical Research Fellow.

UNIVERSITY OF BRISTOL

Dr. A. E. Read has been appointed Lecturer in Medicine.

Dr. T. E. Oppé has resigned the post of Lecturer in Child Health on his appointment as Assistant Director of the Paediatric Unit, St. Mary's Hospital, London.

SOCIETY OF APOTHECARIES OF LONDON

The following candidates, having completed the final examination, have been granted the diploma of L.M.S.S.A.:

A. K. Trounson, E. Aihie, L. B. Oshin, B. R. Collier, J. G. Fairer, C. G. D. Joseph, A. B. Chinnappa, O. Grundstrom, R. Handley, N. C. MacCallum, N. Sabokbar, L. A. B. Murray, G. Dickens, E. M. W. Haire, I. F. Ayad, W. G. S. Russell, J. L. Lane, Y. P. Lee, J. K. C. Chung.

The following candidates have been awarded the Diploma in Mastery of Midwifery:

S. R. Hewitt, J. D. H. Mahoney, A. I. Qureshi, T. A. Rahman.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council of the College held on May 28 with the President, Sir Andrew Claye, in the chair, the following were elected to Council to fill statutory vacancies. As representatives of the Fellows: *London*, Professor J. C. McClure Browne and Mr. S. G. Clayton; *England and Wales (excluding London)*, Mr. F. E. Stabler; *Scotland*, Professor R. J. Kellar; *Northern Ireland and Eire*, Mr. Gavin Boyd. As representatives of the Members: *London*, Mr. J. S. Tomkinson; *Scotland*, Mr. Wallace Barr.

The following were admitted to the Fellowship:

G. H. Bancroft-Livingston, Marjorie O. Bennett, Mary A. M. Bigby, G. W. Blomfield, Joyce M. Burt, W. S. Campbell, E. Cope, H. V. Corbett, G. A. Craig, D. A. Davies, N. S. Devi, J. G. Dumoulin, J. P. Erskine, J. B. Farquhar, G. B. W. Fisher, A. M. Giles, T. A. Gillie, A. M. B. Grant, A. St. G. McC. Huggett, Lois E. Hurter, D. W. James, Mary K. Lawlor, R. F. Lawrence, J. B. Lawson, D. H. Lees, Lorna Lloyd-Green, G. I. Louisson, R. H. Macdonald, Agnes R. Macgregor, K. McI. MacKenzie, C. J. Mackinlay, J. T. Mair, R. McI. Millen, G. Mitchell, P. R. Mitchell, F. L. E. H. Musgrove, P. M. Naidu, M. K. O'Driscoll, E. R. Ormerod, J. H. McK. Pinkerton, E. E. Rawlings, D. N. S. Robertson, C. A. Samad, C. V. Salisbury, D. A. F. Shaw, N. G. G. Talbot, J. M. Thomson, R. Warden.

The following were admitted to the Membership:

A. A. Anklesaria, Alison M. Armstrong, M. P. Awon, Pamela M. Bacon, A. Banerjee, G. S. Banwell, J. D. Begg, K. K. O. Bentsi-Enchill, A. S. Bhandary, K. G. Bland, Kathleen A. S. Brosnan, G. R. Brown, S. Burgin, B. K. Chakrabarti, H. Cohen, J. B. Comerford, F. G. Cox, Gerda J. Crow, M. M. de la Harpe, R. A. Don, Sheila L. B. Duncan, S. Ende, A. C. Fraser, P. H. Foote, K. E. Free, I. K. Furler, W. T. Gallagher, Susan George, R. Giles, C. S. Harison, P. D. Hill, U. Jacobson, S. B. Kamath, P. S. Kan, S. K. Kataria, B. Keane, B. G. Kotwani, A. B. N. Marzuki, T. N. Mitra, T. K.-F. Ng, D. B. Paintin, Heather M. Panton, Mary C. W. Paterson, E. C. Pixley, G. Li. S. Rankin, L. J. Schewitz, S. C. Simmons, N. J. Talati, E. P. W. Tatford, Brenda A. Taylor, Molly E. Towell, Mary M. Tyndall, R. J. Venn, N. F. Walker, W. A. W. Walters, D. K. Williams, L. H. Wright.

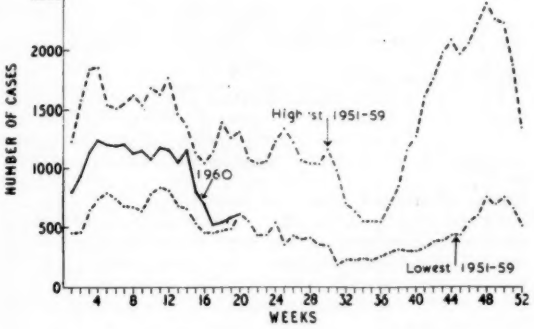
Vital Statistics

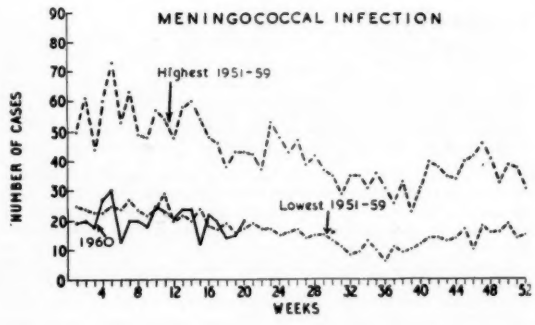
Venereal Diseases

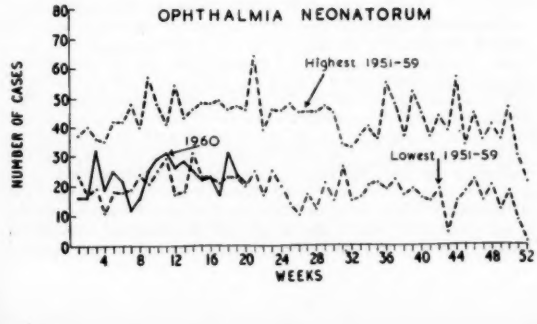
In England and Wales during the quarter ending December 31, 1959, 1,005 new cases of syphilis were reported as attending the clinics, as compared with 1,144 in the previous year. Of these, 235 were classified as primary, secondary, or latent in the first year of infection. Seven cases of congenital syphilis were of children aged under 1 year, and 90 cases in persons over that age. New cases of gonorrhoea (with corresponding 1958 figures in parentheses) numbered 7,627 (7,018), of chancroid 74 (59), and of non-gonococcal urethritis (males only) 5,027 (4,371).—*Monthly Bulletin of the Ministry of Health*, May, 1960.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **May 21** (No. 20) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria ..	2	0	3	0		2	0	4	1	1
Dysentery ..	1,151	141	200	8	11	718	60	179	19	2
Encephalitis, acute	4	0	1	1		3	1		0	
Enteric fever:										
Typhoid ..	1	1	0	0		0	0	0	0	
Paratyphoid ..	12	0	0	0		4	1	1(B)	0	2(B)
Food-poisoning ..	151	29	5	0		208	50	8	0	
Infective enteritis or diarrhoea under 2 years				22	18				8	24
Measles*	1,883	88	39	6	21	17,508	673	353	450	218
Meningococcal infection	20	2	5	1	1	18	4	16	2	3
Ophthalmia neonatorum	21	1	2	0		20	2	1	0	
Pneumonia† ..	250	14	163	3		279	7	146	2	6
Poliomyelitis, acute:										
Paralytic ..	2	0	0	} 0	5	{ 18	6	0	} 0	1
Non-paralytic ..	5	2	0			3	0	2		
Puerperal fever§ ..	209	40	8	1		158	24	13	1	
Scarlet fever ..	620	30	53	20	20	744	39	57	19	24
Tuberculosis:										
Respiratory ..	464	60	73	29		394	34	94	29	
Non-respiratory	67	6	4	3		70	8	10	0	
Whooping-cough	1,458	108	225	3	76	464	17	43	32	69

DEATHS	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	0	0		0		0	0		0	
Encephalits, acute		0			0		1			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	4	0	0	0	0	0	0	0	0	0
Influenza	13	1	5	1	0	8	0	0	0	3
Measles		0	0	0	0		0	1	0	
Meningococcal infection		0	1				0	0		
Pneumonia ..	458	33	21	21	5	337	21	13	10	9
Poliomyelitis, acute	1	0		0	0	0	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	} 49	4	{ 6	2	6	} 61	{ 6	6	1	2
Non-respiratory			2	1	0		0	0	0	0
Whooping-cough	1	0	0	0	0	0	0	0	0	1
Deaths 0–1 year ..	329	34	17	6	7	301	27	24	7	14
Deaths (excluding stillbirths) ..	9,227	734	587	138	142	8,453	652	486	119	158
LIVE BIRTHS ..	16,080	1253	1023	284	463	13,765	1147	1050	284	367
STILLBIRTHS ..	341	19	29			304	18	16		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Royal Faculty of Physicians and Surgeons, Glasgow

H.R.H. Princess ALEXANDRA was admitted to the Honorary Fellowship of the Royal Faculty of Physicians and Surgeons, Glasgow, at a ceremony on June 1. She was sponsored by Professor S. ALSTEAD, the Past-President of the Faculty. In his speech of welcome, Mr. ARTHUR JACOBS, the President, told her that although her royal ancestor, James VI, granted the Charter of Foundation to Peter Lowe in 1599, and her great-grandfather, Edward VII, bestowed on the Faculty the dignity and privileges of a Royal Corporation, hers was the first personal visit by a member of the Royal House. In the evening the President and Fellows of the Royal Faculty entertained Princess Alexandra to dinner and formally presented to her an inscribed plaque for a desk which the Fellows had given to her. Among those presented were Dr. RAE GILCHRIST, P.R.C.P.E., Professor JOHN BRUCE, P.R.C.S.E., and Professor C. M. FLEMING, dean of Glasgow University's medical faculty.

New Physiotherapy Department, Charing Cross Hospital

The old physiotherapy department of Charing Cross Hospital has now moved to spacious and pleasant new quarters in Villiers House, Strand, and these were opened on May 24 by Lord MACKINTOSH OF HALIFAX.

Lord Mackintosh, who was introduced by Lord INMAN OF KNARESBOROUGH, said that physiotherapy was one of the developments in medicine that even the man-in-the-street could understand. It was slow and patient work with none of the quick returns that were reflected in the story of the actor turned surgeon, who, applauded by the onlookers for a deft bit of operating, whipped out the patient's appendix as an encore. Physiotherapy meant an encore day after day. After Lord Mackintosh had unveiled a commemorative plaque, Dr. W. F. DUNHAM, of the allied department of physical medicine, said in the course of a speech of thanks that even in the crowded surroundings of the old physiotherapy department 100,000 treatments had been carried out every year.

Principal, University College of Sierra Leone

The appointment of Dr. DAVIDSON NICOL as principal of the University College of Sierra Leone, Fourah Bay College, was briefly announced in the *Journal*, May 28, p. 1672. Dr. Nicol, who is senior pathologist to the Government of Sierra Leone and directs its Medical Laboratory Services, and Dr. K. O. DIKE, of University College, Ibadan, are the first two African principals of University Colleges in the British Commonwealth.

Dr. Nicol, who was born in Sierra Leone in 1924 and educated in West Africa, went up to Cambridge in 1943 and took first-class honours in Part 2 of the Natural Sciences Tripos in 1947. He qualified in medicine three years later at the London Hospital, where he held resident appointments and was research assistant to Professor J. D'SILVA, of the department of physiology. He went back to West Africa as Lecturer in physiology and biochemistry at University College, Ibadan, Nigeria, for three sessions, and returned to Cambridge in 1954 with a Beit Memorial Fellowship to work with Professor F. G. YOUNG, F.R.S., and Dr. F. SANGER, F.R.S., in the department of biochemistry, proceeding to the degrees of M.D. and Ph.D. of his university, and being elected a Fellow of Christ College, Cambridge, in 1957. He left Cambridge in 1959 for Sierra Leone to join its medical services as senior pathologist, and in 1959 was appointed chairman of the Sierra Leone Library Board and a member of the West African Medical Research Council. Dr. Nicol has published work on tropical malnutrition, the structure and biological activity of insulin peptides, and the tropical anaemias.

Royal College of Physicians, Edinburgh

H.M. QUEEN ELIZABETH THE QUEEN MOTHER, who is an Honorary Fellow of the Royal College of Physicians, Edinburgh, honoured the College in November, 1959, by a visit at which she formally signed the Roll. To commemorate this notable event in the history of the College, the following, among others, have been offered and have accepted the Honorary Fellowship:

Lord ADRIAN, O.M., F.R.S. (formerly vice-chancellor and professor of Physiology, Cambridge University), Sir JOHN BOYD, F.R.S. (president of the Royal Society of Tropical Medicine), Professor J. C. BRAMWELL (formerly professor of cardiology, Manchester University), Lieutenant-General WAJID ALI BURKI (Director-General of Medical Services, Pakistan), Sir HOWARD FLOREY, F.R.S. (professor of pathology, Oxford University), Sir HAROLD HIMSWORTH, F.R.S. (Secretary of the Medical Research Council), Dr. V. R. KHANOLKAR (director of the Indian Cancer Research Centre, Bombay), Dr. W. G. PENFIELD, O.M., F.R.S. (director of the Neurological Institute, Montreal, Canada), Professor E. G. SAYERS (professor of therapeutics, University of Otago, New Zealand).

Royal Medical Benevolent Fund: Giffen House

Giffen House, 15, St. Simon's Avenue, Putney, which was opened in 1959 to provide five rent- and rates-free unfurnished flats for retired married doctors with restricted incomes, has two flats vacant. Applications and inquiries from retired, married doctors are invited and should be addressed to the Secretary, Royal Medical Benevolent Fund, 37, St. George's Road, Wimbledon, London, S.W.19.

The house is situated in a quiet neighbourhood, not far from shops and public transport, and has a pleasant garden. The flats, of two rooms, kitchen, and bathroom, with electric heating, are spacious and entirely self-contained. The only charge is a contribution to the maintenance of the property of £25 a year.

British Cardiac Society

The 39th annual general meeting of the British Cardiac Society was held on May 26 under the chairmanship of Dr. WILLIAM EVANS at the London Hospital. The Society dined together afterwards in the Apothecaries' Hall.

Society of Medical Officers of Health

Dr. G. W. H. TOWNSEND, County Medical Officer of Health, Buckinghamshire, has been elected president of the Society of Medical Officers of Health, and Dr. H. D. CHALKE, Medical Officer of Health, Camberwell, has been re-elected chairman of council of the Society, both for the 1960–1 session.

Continuing Education of Family Doctors

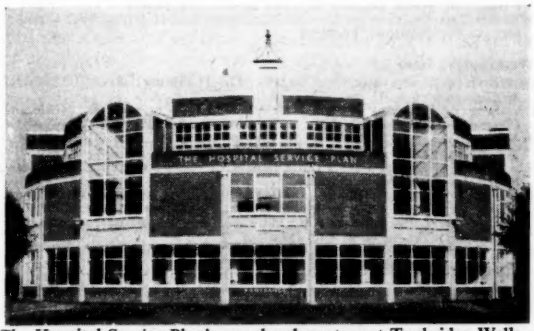
Teaching methods in formal courses for the continuing education of family doctors was the subject of a conference held in London on May 7, organized jointly by the British Postgraduate Medical Federation and the Metropolitan and Home Counties Faculties of the College of General Practitioners with Professor Sir FRANCIS FRASER in the chair.

With the exception of Dr. H. G. MCGREGOR, one of the regional advisers in postgraduate medical education, who spoke from wide personal experience on the organization and administration of these courses, the opening speakers were all general practitioners. Dr. E. A. W. MARIEN asked for concentrated study courses on the basic medical sciences, Dr. G. TABUTEAU suggested ways of making lectures short, pointed, and lively, Dr. J. C. G. EVANS commended clinical demonstrations, and Dr. T. E. A. CARR gave an account of his own experience in arranging standing demonstrations. Dr. H. N. LEVITT has himself organized many symposia, and spoke of the value of this method. He asked that general practitioners should always be included to present their point of view, and went on to give some hints on the arrangement of an "Any Questions?" session. Finally, Dr. R. L. MEYRICK talked about the merits of the clinical pathological conference. Discussion was brisk, and plans for the future were debated with the changing concepts both in medicine and in postgraduate education in mind. The day of the formal lecture was almost over save, perhaps, for an occasional short talk accompanied by a clinical demonstration or ward round on the same subject. The symposium session was generally welcomed, but it was essential for a chosen general practitioner to present the point of view of the family doctor in the discussions. Television as an instructional

medium had its advocates. Many speakers stressed the emotional needs of patients and the training necessary to recognize and meet these needs. It was suggested that changing concepts might cause formal courses to be replaced entirely by other methods. Until then, however, it was generally considered that general practitioners should be co-opted to local committees charged with organizing courses, so that their views might be available during the planning stage.

Hospital Service Plan

The circular building housing the new Head Offices of the Hospital Service Plan was opened at Tunbridge Wells on May 31 by Sir JOHN CHARLES, chief medical officer to the Ministry of Health, in the presence of the chairman, Sir RUSSELL BRAIN, and other distinguished guests.



The Hospital Service Plan's new headquarters at Tunbridge Wells.

Membership of the Hospital Service Plan, founded in 1943 to enable contributors to provide for the expenses of private treatment, has increased by more than 100% in the last five years and the new building, at 157, St. John's Road, Tunbridge Wells, Kent, allows for further expansion. The London office in the B.M.A. building is being retained.

"Journal of Child Psychology and Psychiatry"

The new quarterly, *Journal of Child Psychology and Psychiatry*, is the official organ of the Association of Child Psychology and Psychiatry. The journal will be primarily concerned with these subjects, but it is recognized that many other disciplines have an important contribution to make in furthering knowledge of the mental life and behaviour of children, and relevant papers will accordingly be welcomed from such related fields as animal behaviour, anthropology, education, family studies, paediatrics, physiology, and sociology. The journal will be edited jointly by Dr. EMANUEL MILLER, and by Mr. C. B. HINOLEN, research psychologist, and Miss ELIZABETH IRVINE, psychiatric social worker. Further details may be obtained from the publishers, Pergamon Press Ltd., Headington Hill Hall, Oxford. The annual subscription rates are, to members of the A.C.P.P., £3 3s., inclusive of membership, to private individuals £5 5s. ($15), and to libraries and institutions £7 ($20) a volume.

Art and Psychopathology

The Société Internationale de Psychopathologie de l'Expression has recently been founded, under the presidency of Professor JEAN DELAY, professor of psychiatry in the University of Paris and a member of the Académie Française. The Society's activities include scientific meetings and conferences at which exhibitions are held of works of art which are of particular interest to psychologists. The annual conference for 1960 will be held in Catania, Sicily, on October 7–10. Particulars of the Society may be had from Dr. G. M. CARSTAIRS, Room 329, Tavistock House South, Tavistock Square, London, W.C.1.

"Clinical Science": Change of Management

Clinical Science will shortly be produced jointly by the Medical Research Society and the Biochemical Society. It is hoped that, in addition to maintaining existing interests, the journal will attract an increased proportion of papers of a metabolic or biochemical character in the clinical field. The reconstituted journal, published by the Cambridge University Press, will consist of six numbers a year, the first appearing in February, 1961. Contributions should be addressed to the editor and editorial board's chairman, Professor G. M. BULL, Queen's University, Belfast, Institute of Clinical Science, Grosvenor Road, Belfast, N. Ireland.

Register of Chiropodists

The 1960 *National Register of Medical Auxiliary Services: Chiropodists* has now been published by the Board of Registration of Medical Auxiliaries. Copies of the *Register* will be sent free to members of the medical profession, hospitals, and official bodies on application to the Registrar, Board of Registration of Medical Auxiliaries, B.M.A. House, Tavistock Square, London, W.C.1.

Saint Vincent International Prize for Medical Science

This prize, worth approximately £6,000, is offered by the Medical Academy of Turin for important contributions to the development of medical science. It can be awarded to a single research-worker or to a group collaborating in the same field. Details may be obtained from Professor G. BALDINI, Istituto Italiano di Cultura, 39, Belgrave Square, London, S.W.1.

John Holt Medal

The John Holt Medal, which was awarded by the Liverpool School of Tropical Medicine to Sir SAMUEL MANUWA for distinguished services to tropical medicine, was presented to him last February in Government House, Lagos, Nigeria, by the GOVERNOR-GENERAL, who also read a personal congratulatory letter from the DUKE OF EDINBURGH (the Patron of the School). The citation was read by the Dean of the School, Professor B. G. MAEGRAITH.

T.A.M.O.s' Association

Colonel F. H. BLACKBURN, T.D., has been elected President of the Territorial Army Medical Officers' Association in place of Brigadier W. R. WARD, T.D., who has retired.

Edinburgh Courses in Radiological Health

Three-year postgraduate courses in radiological health and safety for students with honours science degrees will start at Edinburgh University in October. Similar courses, in line with the recommendations of the Fleck Committee, have already been established at London and Birmingham Universities.

In Brief

The introduction of plastic syringes, which can be discarded after being used once, has been approved by Aberdeen Health and Welfare Committee at an additional annual cost of £3,425.

London County Council estimates that the London ambulance service and the home-help service will cost over £1m. each to maintain in 1960–1.

Doctors, surgeons, and architects attended the memorial service at St. Pancras Church on June 2 of Dr. CHARLES HOLDEN, who died on May 1, aged 85. He designed the British Medical Association building in the Strand, with its Epstein statues, as well as many hospitals, university buildings, and much of the London Underground.

People in the News

Dr. L. GUTTMANN, director of the National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury, has received the 1960 International Prize of the Spanish Association for Invalids and the Handicapped, awarded for outstanding humanitarian work. The prize has previously been awarded to Dr. ALBERT SCHWEITZER and Dr. J. SALK.

Dr. JAMES KENNEDY, who retired last year after 27 years as the Government medical officer in the Ndanga district of S. Rhodesia, has been awarded the Bronze Medal of the Royal African Society, which is given for "dedicated service to Africa."

Dr. J. F. RILEY has been invited to open the symposium on mast cells at the Canadian Federation of Biological Societies' Winnipeg meeting in June.

COMING EVENTS

Mitchell Lecture.—Dr. J. G. SCADDING: "Mycobacterium Tuberculosis in the Aetiology of Sarcoidosis." Details on advertisement p. 63.

British Institute of Radiology.—Meeting in the Reid-Knox Hall of the Institute, 32, Welbeck Street, London, W.1, June 17, 2–5.30 p.m. Short papers on work in progress in radiobiology will be read. Details from the Institute at the above address.

Royal College of Surgeons, Edinburgh.—Professor R. B. DUTHIE (professor of orthopaedic surgery, University of Rochester, New York): "The Histochemistry of Bone Repair." June 22, 5 p.m. The lecture, in the College Hall, is open to postgraduate students.

West London Medico-chirurgical Society.—Annual banquet, June 24, 7.30 p.m., the Harcourt Rooms, House of Commons. Members wishing to visit the Houses of Parliament should arrive not later than 6.45 p.m. Numbered tickets (35s. exclusive) from Honorary Secretaries of the Society, West London Hospital, Hammersmith, London, W.6.

Royal College of Surgeons in Ireland Faculty of Anaesthetists.—Inaugural Scientific Meeting, Symposium: "Levels of Anaesthesia," in the College, St. Stephen's Green, Dublin, July 9, 10 a.m. Fee for meeting, including lunch and refreshments, £1 10s. Applications to Registrar, Royal College of Surgeons in Ireland, St. Stephen's Green, Dublin, before July 4.

Postgraduate Medical School and Hammersmith Hospital Association.—Annual dinner and dance, Park Lane Hotel, July 8, 7.30 p.m. Details from Dr. M. K. SYKES, Department of Anaesthetics, Hammersmith Hospital, London, W.12.

Postgraduate Medical School, London.—Symposium for consultants, "Diagnosis and Treatment for the Chronic Arthritides," September 22 and 23. Details on advertisement p. 62.

NEW ISSUES

BRITISH JOURNAL OF OPHTHALMOLOGY

Lattice Dystrophy of the Cornea. A. J. Dark and D. S. Thomson.
The Central Artery of the Retina. II. Distribution and Anastomoses. S. Singh and R. Dass.
Keratomalacia Associated with Adrenal Hypoplasia in a Defective. M. H. Mullins.
Amaurosis after Occlusion of the Internal Carotid Artery Treated by Cyclodiathermy. C. McCulloch.
Orbital Meningo-encephalocoele and Exophthalmos. A. Mortada and I. El-Toraei.
New Instruments for Use in Cataract Extraction. F. Silván.
Correspondence.
Reviews.

Volume 44, No. 5. (Monthly; £6 annually. With "Ophthalmic Literature" and Index, £9.)

BRITISH JOURNAL OF INDUSTRIAL MEDICINE

Dust Content, Radiology, and Pathology in Simple Pneumoconiosis of Coalworkers. Part I: General Observations. D. Rivers, M. E. Wise, E. J. King, and G. Nagelschmidt. **Part II: Detailed Analysis of the Data.** D. Rivers and M. E. Wise.
Pneumoconiosis in Makers of Artificial Grinding Wheels, Including a Case of Caplan's Syndrome. E. Posner.
A Study of the Repeatability of Ventilatory Tests, Anthropometric Measurements, and Answers to a Respiratory Symptoms Questionnaire in Working Coal-miners. J. R. Ashford, G. D. Forwell, and R. Routledge.
A Study of the Reproducibility of the Forced Vital Capacity of Coal-workers at Two Collieries in Scotland and Two Collieries in South Wales. D. P. Duffield and J. R. Ashford.
Antiseptic Cream for Use on the Hands in Food Establishments. Doreen L. Wedderburn.
Oil Folliculitis: A Study of 200 Men Employed in an Engineering Factory. J. S. Finnie.
Studies on the Chemical Forms of Urinary Lead. G. T. Dinischiotu, B. Nestorescu, I. C. Radulescu, C. Ionescu, N. Preda, and G. Ilutza.
Effects of Chronic Dieldrin Ingestion on the Muscular Efficiency of Rats. Mélèk Khaïry.
The Failure of Absorption of DC Silicone Fluid 703 from the Gastro-intestinal Tract of Rats. J. Paul and W. F. R. Pover.
The Origin of the Term "Pneumonokoniosis." A. Meiklejohn.
Obituary: Dr. Sydney Henry.
Book Reviews.

Volume 17, No. 2. (Quarterly; £3 annually.)

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, June 13

CAMBRIDGE UNIVERSITY POSTGRADUATE MEDICAL SCHOOL.—At Radiotherapeutic Centre, Addenbrooke's Hospital, 4 for 4.15 p.m., Professor J. Romano (Rochester University, U.S.A.): Teaching of Psychiatry to Medical Students.
INSTITUTE OF DERMATOLOGY.—At British Institute of Radiology, 5 p.m., Dr. P. Wade: Radiotherapy of Malignant Skin Conditions, I.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—6 p.m., Dr. Catherine Smith (St. Louis): Cytology of the Membranous Labyrinth.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. Brian Ackner: Psychiatric Aspects of Termination of Pregnancy.

Tuesday, June 14

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Mr. Aleck Bourne: Troubles of the Menopause.
WILLIAM TEMPLE ASSOCIATION.—At 24, South Audley Street, W., 8 p.m., Mr. A. W. Peterson: Penology.

Wednesday, June 15

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Recent Advances in Histopathology of the Skin.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Professor R. Neubauer (Yugoslavia): Role of B.C.G. in Tuberculosis Control.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. D'Arcy Hart: Tuberculin Reaction.
ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.—5.15 p.m., Dr. J. B. West: Pulmonary Function in Disease.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., Renal Association 10th Anniversary Lecture by Dr. H. Wirz (Basle, Switzerland): Mechanism of Urinary Concentration and Dilution.

Thursday, June 16

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. R. M. Mason: Spondylitis.
ROYAL SOCIETY OF HEALTH.—At Civic Theatre, Bedford, 10.30 a.m., Dr. C. L. E. H. Sharp: Fluoridation—A Layman's Guide to an Advance in Preventive Medicine.
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At 26, Portland Place, W., 7.30 p.m., annual general meeting followed by ordinary meeting. Sir Philip Manson-Bahr: Around the World in 35 Days (illustrated).
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., postgraduate demonstration by Dr. D. Curran: Psychiatry.

Friday, June 17

BRITISH INSTITUTE OF RADIOLOGY: ROENTGEN SOCIETY.—8 p.m., radiobiology meeting.
INSTITUTE OF CARDIOLOGY.—At Barnes Hall, Royal Society of Medicine, 5 p.m., St. Cyres Lecture by Sir Russell Brock: Surgical Treatment of Pulmonary Stenosis.
●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. H. Meara: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. K. F. W. Hinson: clinical demonstration.
KENT AND CANTERBURY HOSPITAL.—8 p.m., clinical meeting.
LONDON UNIVERSITY.—At Barnes Hall, Royal Society of Medicine, 5 p.m., St. Cyres Lecture of Institute of Cardiology by Sir Russell Brock: Surgical Treatment of Pulmonary Stenosis.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. P. S. London: Some Aspects of the Care of Wounds.

APPOINTMENTS

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—G. S. Foster, M.D., M.R.C.O.G., Consultant Obstetrician and Gynaecologist to Weston-super-Mare Group of Hospitals; D. T. Gordon, M.B., Ch.B., D.P.H., Senior Hospital Medical Officer in Infectious Diseases to Scott Isolation Hospital, Plymouth; D. L. Pryer, M.B., B.S., F.F.A. R.C.S., Consultant Anaesthetist to Torbay Area; R. K. Roddie, M.B., B.Ch., F.R.C.S., Consultant Ear, Nose, and Throat Surgeon to Bristol Clinical Area; D. H. K. Soltau, M.B., B.Chir., F.R.C.S., M.R.C.O.G., Consultant Obstetrician and Gynaecologist, and D. S. Thomson, M.B., B.S., D.O.M.S., F.R.C.S.Ed., Consultant Ophthalmic Surgeon, both to North Gloucestershire Clinical Area; R. S. Bhonsle, M.B., B.S., Registrar in Ear, Nose, and Throat Surgery to South Devon and East Cornwall Hospital, Plymouth; M. S. I. Chandra Sekaran, M.B., B.S., D.L.O., Registrar in Ear, Nose, and Throat Surgery to Bath Group of Hospitals (re-appointed); L. D. Heap, M.R.C.S., L.R.C.P., Registrar in Pathology to Bath Group of Hospitals; Helen S. Mathewson, M.B., Ch.B., D.P.M., Registrar in Child Psychiatry and Mental Deficiency, Hortham-Brentry Group.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Le Geyt.—On May 24, 1960, Daniel Edward Le Geyt, M.R.C.S., L.R.C.P., of Tintagel, Cornwall, formerly of Jersey.
Lobban.—On May 24, 1960, in hospital, George Mackenzie Davidson Lobban, M.B., Ch.B., D.P.H., of Lewes House, Lewes, Sussex, aged 64.
Patton.—On May 23, 1960, at Bideford District Hospital, Bideford, Devon, Walter Scott Patton, M.B., Ch.B., Major, I.M.S., retired, of Torrington, Devon, formerly of Liverpool, aged 83.
Roch.—On May 23, 1960, in Belfast, Horace Sampson Roch, C.M.G., C.B.E., D.S.O., M.R.C.S., L.R.C.P., Colonel, late R.A.M.C., retired, of Woodbine Hill, near Youghal, Co. Cork, aged 83.
Thompson.—On May 15, 1960, at Old Pembury Court, Pembury, Kent, Ralph Reakes Thompson, *M.C.*, M.R.C.S., L.R.C.P., Lieutenant-colonel, R.A.M.C., retired, aged 69.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Reaction to T.A.B.T.

Q.—*A patient had a fairly severe general feverish reaction after the first T.A.B.T. injection. Should the second injection be omitted, or a reduced dosage given ?*

A.—One might ask: "Will the patient be likely to run unnecessary risks if he is not vaccinated with T.A.B. ? The patient's age and previous immunization with T.A.B. (in the Services or elsewhere) are not mentioned, but it is known that repeated doses of enteric vaccines induce a hypersensitivity state in certain subjects; older persons are sometimes even excluded from these inoculations. If, therefore, T.A.B. vaccine can be dispensed with, the immunization against tetanus alone can proceed normally.

The constituent of the mixed prophylactic which caused the reaction is almost certainly the T.A.B. vaccine. If it is desirable to proceed with immunization with T.A.B., the second dose should be 0.1 ml., given *intradermally*: one reinforcing dose, of the same amount, should be administered intradermally about six months later. Reactions to these doses are likely to be much less severe. Quite independently immunization against tetanus should be continued with tetanus toxoid. The intradermal T.A.B. should be given four weeks after the T.A.B.T. which caused the reaction ; the tetanus toxoid should not be administered until six weeks have elapsed, and should be followed by a third dose after a further six to 12 months.

Sterilizing Sharp Instruments

Q.—*What is the best method of sterilizing sharp instruments (1) under hospital conditions, and (2) under conditions in the African bush ? Is soaking in lysol or "dettol" (pure) adequate ?*

A.—The answer depends on whether absolute sterility is required, or only freedom from vegetative bacteria, as distinct from spores. If the former, a high-pressure high-speed instrument autoclave provides the best method: the whole of the instruments required for an operation, sharp or otherwise, can be sterilized in six minutes and without damage. Dry heat is sometimes used, but causes some damage by oxidation: an electric oven which rapidly takes instruments to a high temperature in an atmosphere of nitrogen is now being developed which overcomes this objection. The only chemical germicide which will absolutely sterilize without damaging steel is formalin: immersion for six hours in a solution containing at least 2.5% of formalin and an anti-rusting agent is necessary.

Presumably instruments already sterilized could be taken into the African bush, but if they have to be dealt with on the spot and quickly, the only possibility is a chemical method which will destroy vegetative bacteria only. Provided that the instruments are quite clean, 75% spirit or an adequate concentration of any phenolic germicide will serve the purpose. Spirit can be reinforced by including 0.5% of chlorhexidine ("hibitane"). Of the two phenolic germicides mentioned, lysol is the more dependable for this purpose, and need not be used in any concentration exceeding 5%.

Non-specific Urethritis

Q.—*A man aged 50, with a history of non-specific urethritis 20 years ago, now has a thin, glairy urethral discharge, particularly after an erection. Prostatic fluid after massage is sterile. What treatment would be helpful ?*

A.—If treatment is to be effective the cause of the condition must be established by full investigation. The secretion should be examined microscopically and by culture to determine whether it is due to an inflammatory process and to identify or exclude the presence of causative organisms. The urine should be collected with sterile precautions and examined with the naked eye, by microscopy after centrifugation, and by culture. All these specimens are best taken in the early morning when the urine has been held from the night before. General examination should determine whether the bladder is distended, and rectal examination whether the prostate is enlarged or shows changes suggestive of old chronic prostatitis or of neoplasm. Anterior urethroscopy may show stricture which requires dilatation, and the passage of a full-size metal sound will exclude stricture in the posterior urethra. If there is considerable pus in both specimens of urine in the two-glass test, cystoscopy and intravenous pyelography should be done. If the urethral secretion contains pus cells, no causative organism is identified, and the investigations give no evidence of an underlying cause, the diagnosis is "non-specific" urethritis. This may be a primary condition or secondary to prostatitis of long standing. Remedies most likely to be effective are broad-spectrum antibiotics such as tetracycline or oxytetracycline, and the effective dosage is 250 mg. by mouth every six hours for 20 doses. After the urethritis has responded the prostatic fluid should be examined microscopically to determine whether the patient has prostatitis, for which further treatment may be required.

Magnesium Estimations

Q.—*What are the indications for magnesium estimations, and are they frequently done ?*

A.—Magnesium deficiency has been described after prolonged losses of intestinal fluids, from fistulous discharge, or diarrhoea.[1] It takes a month or more to develop to a significant degree. Deficiency may occasionally account for tetany, but the principal symptoms are irritability and apprehension, tremors, and twitching. An excess of magnesium may accumulate in the body with renal failure.[2] The ion is not estimated very often in clinical practice, because methods have not been suitable for routine use. Good methods are now available.[3]

REFERENCES

1 Randall, R. E., Bleifer, K. H., and Rossmeisl, E. C., *Ann. intern. Med.*, 1959, **50**, 257.
2 Smith, W. O., and Hammarsten, J. F., *A.M.A. Arch. intern. Med.*, 1958, **102**, 5.
3 Wilkinson, R. H., *J. clin. Path.*, 1957, **10**, 126.

Swimming in Chlorinated Water

Q.—*A 15-year-old girl who is a keen swimmer suffers from an acute sinusitis and rhinitis after swimming in chlorinated water. Is there any way of mitigating the effects of the chlorine other than giving up swimming ?*

A.—The only way of mitigating the effects of chlorinated water in a person whose nose is sensitive to it is to ensure in some way that the chlorine does not enter the nose. Simple nose-clips are available, and some swimming-baths are treated with ultra-violet light instead of chlorine. The patient may, of course, swim in sea-water.

Vagitus Uterinus

Q.—*When rupturing the membranes I and several trained witnesses distinctly heard without a stethoscope intrauterine foetal crying. How often has this been observed ?*

A.—From early days vagitus uterinus, as this phenomenon is called, has been recognized to occur, albeit rarely. Formerly internal version was the most common manœuvre at which air was introduced into the uterus, but more recently cases have been reported after the artificial and even the spontaneous rupture of the membranes. The theory is that the air carried into the uterus is inhaled by the foetus and then either expired or expressed by uterine contraction so as to be heard as a cry. The literature on this subject was reviewed by Ryder,[1] and more recently Crotty and Kuehnle[2] described its occurrence in twin

pregnancies. In this country a case report by Curphey[3] elicited correspondence from others who had heard intrauterine crying.

REFERENCES

1 Ryder, G. H., *Amer. J. Obstet. Gynec.*, 1943, **46**, 867.
2 Crotty, J. G., and Kuehnle, L. W., ibid., 1948, **56**, 977.
3 Curphey, E., *Brit. med. J.*, 1947, **2**, 508.

Blood Volume and Polycythaemia Vera

Q.—*Is the estimation of blood volume the most important test in the laboratory diagnosis of polycythaemia vera? What is the most practicable method of doing this estimation in a small laboratory?*

A.—The estimation of the blood volume is extremely useful in polycythaemia vera, but it is subject to exactly the same difficulty in interpretation as are haemoglobin and haematocrit. In typical cases, polycythaemia vera can be diagnosed quite easily on clinical grounds and an estimation of haemoglobin and haematocrit, and it is only in cases where the polycythaemia is minimal that difficulty arises.

In these cases one needs to determine the circulating red-cell mass rather than the plasma volume, and this requires the use of radioactive labelling, preferably with ^{51}Cr, a procedure which is not suitable for a small laboratory. Indirect estimations from the plasma volume and the haematocrit are much less reliable, but they can be used, and the method used by Mollison[1] is probably the best for routine purposes.

REFERENCE

1 Mollison, P. L., *Blood Transfusion in Clinical Medicine*, second edition, 1956. Oxford.

Phenylketonuria

Q.—*What is the aetiology of phenylketonuria and how is it diagnosed? By what age should the condition be recognized for treatment to be successful?*

A.—Phenylketonuria is thought to be a hereditary disease transmitted by a recessive gene. Siblings and other relatives, such as cousins and uncles, may be affected, but the parents are free from the disease, although it has been described in two cases in the United States to have affected the mother. The risk of a child manifesting this disease in an affected family will therefore be about 1 in 4.

Diagnosis depends on a positive test for phenylpyruvic acid in the urine. Clinically the diagnosis should be suspected in infancy in a baby who is delayed in development and who is fair-haired. Dark hair may occur in occasional cases but is very unusual. An older child is more severely mentally retarded, may suffer from fits, but has no characteristic appearance apart from fair hair and perhaps a tendency to wide spacing of the teeth.

The earlier the condition is recognized the more successful treatment is likely to be. It is therefore important to diagnose it in the first two months of life, if it is possible to do so, in order to get the best result. After the age of 3 or 4 months it is likely that some permanent degree of damage to the brain will have occurred. However, it is not possible to diagnose the condition in the first days of life, and it is only very occasionally that phenylpyruvic acid appears in the urine by the age of 10 days. In many cases it is not present in sufficient concentration to give a positive test until about 6 weeks of age, when 85 to 90% of cases will give a positive result on testing.

The usual test for phenylpyruvic acid is a ferric chloride test. Urine is acidified with a few drops of 2% sulphuric acid and ferric chloride solution (10% liquor ferri perchlor.). The urine turns a green colour. A very simple way of testing for phenylpyruvic acid is by using "phenistix." The phenistix needs only to be dipped in some urine or pressed between the layers of a damp napkin, when it will change colour if phenylpyruvic acid is present. The diagnosis can be further confirmed by finding a raised level of phenylalanine in the blood. This condition is very well described by Hilliard and Kirman.[1]

REFERENCE

1 Hilliard, L. T., and Kirman, B. H., *Mental Deficiency*, 1957. Churchill, London.

Eczema After Vaccination

Q.—*A man developed a generalized weeping eczema six weeks after smallpox vaccination. He improved on oral antihistamines and hydrocortisone ointment but relapsed, and now, two months later, still has a rash. Could this be attributed to vaccination? Could any line of treatment be suggested which might benefit the patient?*

A.—In the predisposed, it is well recognized that vaccination may precipitate an attack of eczema which may then persist as a constitutional disorder. The problem here now calls for general medical consideration, overhaul of the patient, attention to any sources of stress from within or without, and investigation of any sources of sensitization, specific or otherwise. The eczema itself should be treated along the usual lines with soothing and antipruritic measures locally, and the avoidance of external irritation and perhaps of washing. Internally small doses of sedative to relieve irritation will help.

Flaking of the Nails

Q.—*What is the cause of flaking of the nails, and what can be done for it?*

A.—Flaking of the nails is a common complaint. It is aggravated by the use of nail varnish and perhaps more particularly of varnish remover, but apart from this I cannot identify any cause. Successful treatment is the use of friction, which can be conveniently applied by polishing the nails with a wash-leather buffer for 5 or 10 minutes daily. In the course of a few months the nails will usually thicken and harden sufficiently to prevent further trouble. The treatment, of course, has to be continued.

Numbering the Rings

Q.—*What convention is observed in numbering the rings of complex organic compounds?*

A.—The official convention is that one begins to number on the top right-hand corner, and proceeds clockwise. There are, however, numerous exceptions. These have arisen for historical reasons, and apply mostly to biological compounds. For instance, purines begin to be numbered at the top left-hand corner and go around the first ring anti-clockwise and continue in the second ring clockwise. Steroids have a numbered sequence all of their own. On the other hand, not even riboflavin is numbered in the orthodox manner. Details of this rather confused situation can be looked up in *International Union of Pure and Applied Chemistry Nomenclature of Organic Chemistry, 1957* (Butterworth, London, 1957).

Correction.—We regret that in the article "Translating from Russian" (May 21, p. 1561) the name of the editor of the *Russian-English Medical Dictionary* by Stanley Jablonski was given as B. S. Levene; this should have read B. S. Levine.

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